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(71) Applicant *(for all designated States except US)*: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: RICHTER, Stefan, Lutz [DE/DK]; Sødalen 15, DK-2820 Gentofte (DK). MADSEN, Kjeld [DK/DK]; Ny Vestergaardsvej 3, DK-3500 Værløse (DK). THØGERSEN, Henning [DK/DK]; Gregersmindevej 8, DK-3520 Farum (DK). JOHANSEN, Nils, Langeland [DK/DK]; Tibbevangen 78, DK-2730 Herlev (DK). HANSEN, Annette [DK/DK]; Elmekrogen 13, DK-3500 Værløse (DK). OLSEN, Ole, Hvilsted [DK/DK]; Bækkeskovvej 38, DK-2700 Brønshøj (DK). ANDERSEN, Peter, Høngaard [DK/DK]; Rødtjørnevej 28, DK-2720 Vanløse (DK).

(74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).

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(54) Title: COMPOUNDS WITH GROWTH HORMONE RELEASING PROPERTIES

(57) Abstract

The present invention relates to truncated GHRs of general formula (I): K-$(M)_x$-A-B-$(C)_w$-D-E-$(F)_z$-G-$(N)_y$-L which have the ability to stimulate release of endogenous growth hormone.

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COMPOUNDS WITH GROWTH HORMONE RELEASING PROPERTIES

FIELD OF INVENTION

The present invention relates to novel compounds, compositions containing them, and their use for treating medical disorders resulting from a deficiency in growth hormone.

BACKGROUND OF THE INVENTION

Growth hormone is a hormone which stimulates growth of all tissues capable of growing. In addition, growth hormone is known to have a number of effects on metabolic processes, e.g., stimulation of protein synthesis and free fatty acid mobilization and to cause a switch in energy metabolism from carbohydrate to fatty acid metabolism. Deficiency in growth hormone can result in a number of severe medical disorders, e.g., dwarfism.

Growth hormone is released from the pituitary. The release is under tight control of a number of hormones and neurotransmitters either directly or indirectly. Growth hormone release can be stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin. In both cases the hormones are released from the hypothalamus but their action is mediated primarily via specific receptors located in the pituitary. Other compounds which stimulate the release of growth hormone from the pituitary have also been described. For example arginine, L-3,4-dihydroxyphenylalanine (L-Dopa), glucagon, vasopressin, PACAP (pituitary adenylyl cyclase activating peptide), muscarinic receptor agonists and a synthethic hexapeptide, GHRP (growth hormone releasing peptide) release endogenous growth hormone either by a direct effect on the pituitary or by affecting the release of GHRH and/or somatostatin from the hypothalamus.

In disorders or conditions where increased levels of growth hormone is desired, the protein nature of growth hormone makes anything but parenteral administration non-viable. Furthermore, other directly acting natural secretagogues, e.g., GHRH and PACAP, are longer polypeptides for which reason oral administration of them is not viable.

The use of certain compounds for increasing the levels of growth hormone in mammals has previously been proposed, e.g. in EP 18 072, EP 83 864, WO 89/07110, WO 89/01711, WO 89/10933, WO 88/9780, WO 83/02272, WO 91/18016, WO 92/01711, WO 93/04081, WO 95/17422, WO 95/17423 and WO 95/14666.

The composition of growth hormone releasing compounds is important for their growth hormone releasing potency as well as their bioavailability. It is therefore an object of the present invention to provide novel compounds with growth hormone releasing properties.

Summary of the invention

The present invention relates to compounds of the general formula I

$$K\text{-}(M)_x\text{-}A\text{-}B\text{-}(C)_w\text{-}D\text{-}E\text{-}(F)_z\text{-}G\text{-}(N)_y\text{-}L$$

(I)

wherein K, M, A, B, C, D, E, F, G, N, L, x, w, z and y are as defined below.

The compounds of formula I have the ability to stimulate synthesis and/or release of endogenous growth hormone. Thus, these compounds can be used in the treatment of conditions which require stimulation of growth hormone production or

secretion such as in humans with growth hormone deficiency or were increased growth hormone plasma levels is desired like in the elderly or in animals used for food production.

Description of the invention

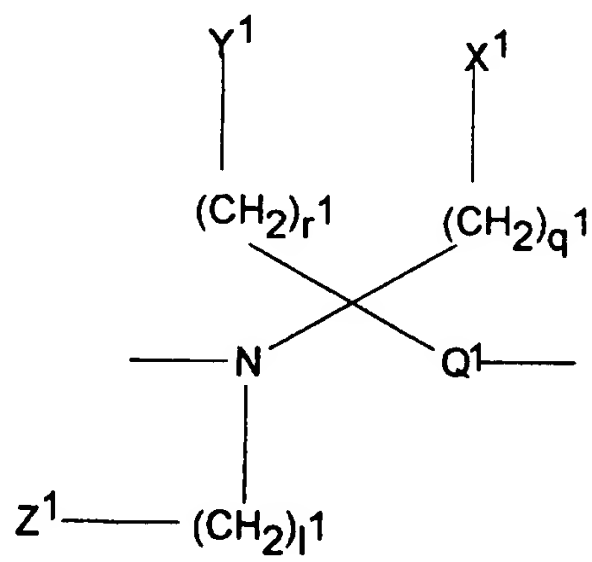
The present invention relates to a compound of the general formula I

$$K\text{-}(M)_x\text{-}A\text{-}B\text{-}(C)_w\text{-}D\text{-}E\text{-}(F)_z\text{-}G\text{-}(N)_y\text{-}L$$

(I)

wherein z and w are independently 0 or 1,

A and D are independently a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula II



formula II

wherein Q^1 is $-CH_2-$ or -CO-,

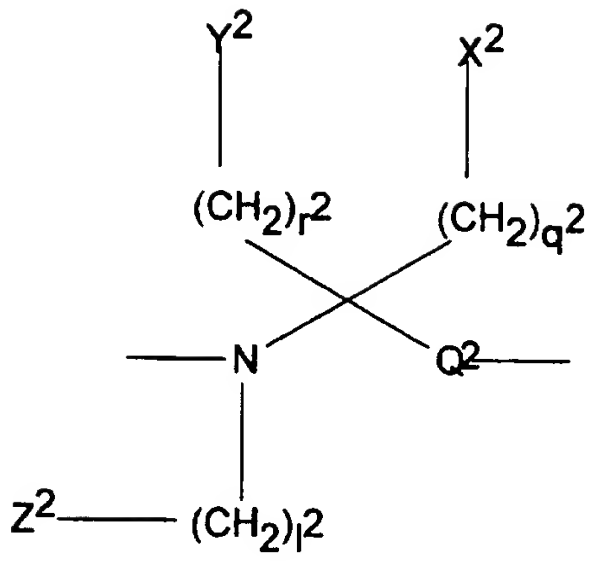
l^1 ,q^1 and r^1 are independently 0, 1, 2, 3, 4, 5, or 6,

X^1 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

Y^1 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^1 or Z^1

Z^1 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

B, C, E, F are independently a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 , q^2 and r^2 are independently 0, 1, 2, 3, 4, 5, or 6,

X^2 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

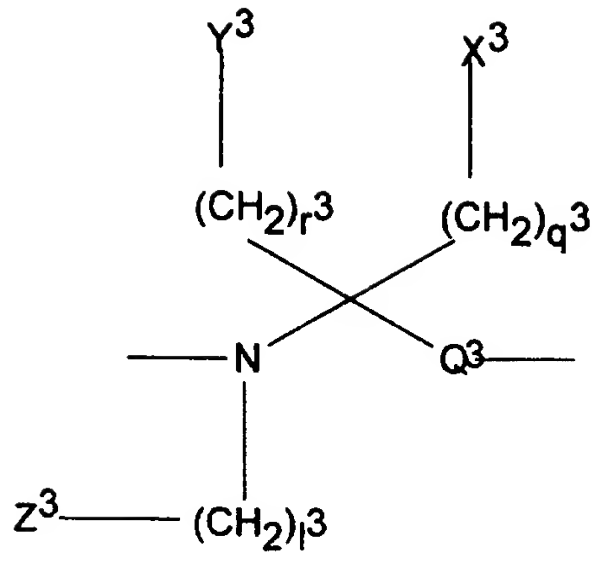
Y^2 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^2 or Z^2,

Z^2 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy,

carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond;

or the residues of any of the following, non-proteinogenic amino acids (R- and S-isomer for chiral amino acids) dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, 3-amino-1,2,4-triazole-5-carboxylic acid, 1,2,3,4-tetrahyroisoquinoline-3-carboxylic acid, aminobiphenyl-carboxylic acids, pipecolic acid, nipecotinic acid, isonipecotinic acid, statine, 4-amino-3-hydroxybutyric acid, aminohexanoic acid, 2-amino-2-thiazoline-4-carboxylic acid, 1,2,3,4-tetrahyronorharman-3-carboxylic acid, 3-amino-3-methyl-benzoic acid, 3-aminomethylbutanoic acid, 5-aminopentanoic acid, 2-amino-thiazoleacetic acid, 2-aminothiopheneacetic acid, cis- and trans 2-amino-cyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid, 4-amino-methylbenzoic acid, aminonaphthoic aicd, aminopenicillanic acid, 3-aminopyrazole-4-carboxylic acid, 2-amino-4-pentenoic acid, 2-aminothiopheneacetic acid, 3-aminobutyric acid, aminolevulinic acid, 8-aminocaprylic acid;

G is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula IV



formula IV

wherein Q^3 is $-CH_2-$ or -CO-,

l^3, q^3 and r^3 are independently 0, 1, 2, 3, 4, 5, or 6,

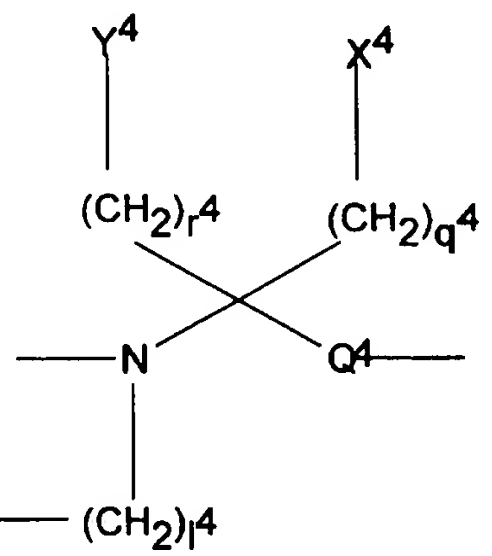
X^3 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

Y^3 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^3 or Z^3,

Z^3 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy,

carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

M is an amino acid residue, a dipeptide residue, a tripeptide residue, a tetrapeptide residue, a pentapeptide residue, a hexapeptide residue, a heptapeptide residue, a octapeptide residue, a nonapeptide residue, a decapeptide residue, a undecapeptide residue, a dodecapeptide residue or a tredecapeptide residue, wherein the amino acid residues are independently any non-proteinogenic or proteinogenic alpha amino acid residue of the general formula V



formula V

wherein Q^4 is $-CH_2-$ or -CO-,

l^4, q^4 and r^4 are independently 0, 1, 2, 3, 4, 5, or 6,

X^4 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy,

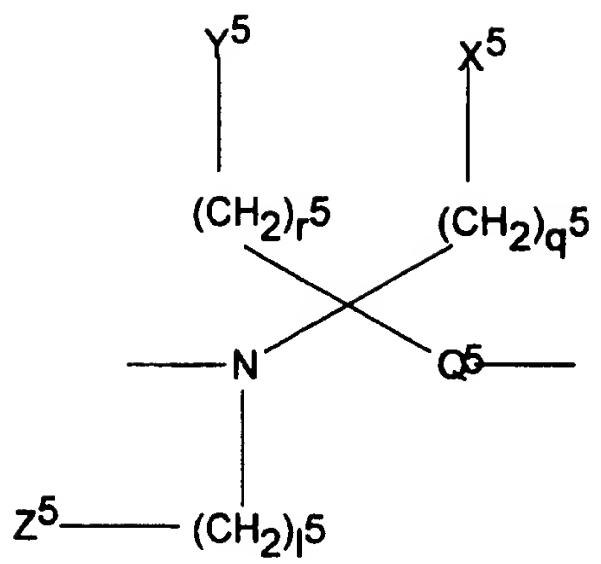
carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

Y^4 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^4 or Z^4,

Z^4 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond;

or the residues of any of the following, non-proteinogenic amino acids (R- and S-isomer for chiral amino acids) dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, 3-amino-1,2,4-triazole-5-carboxylic acid, 1,2,3,4-tetrahyroisoquinoline-3-carboxylic acid, aminobiphenyl-carboxylic acids, pipecolic acid, nipecotinic acid, isonipecotinic acid, statine, 4-amino-3-hydroxybutyric acid, aminohexanoic acid, 2-amino-2-thiazoline-4-carboxylic acid, 1,2,3,4-tetrahyronorharman-3-carboxylic acid, 3-amino-3-methyl-benzoic acid, 3-aminomethylbutanoic acid, 5-aminopentanoic acid, 2-amino-thiazoleacetic acid, 2-aminothiopheneacetic acid, cis- and trans 2-amino-cyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid, 4-amino-methylbenzoic acid, aminonaphthoic aicd, aminopenicillanic acid, 3-aminopyrazole-4-carboxylic acid, 2-amino-4-pentenoic acid, 2-aminothiopheneacetic acid, 3-aminobutyric acid, aminolevulinic acid, 8-aminocaprylic acid ;

N is an amino acid residue, a dipeptide residue, an oligopeptide residue or an oligoamide residue which is between 1 to 10 amino acid residues long wherein the amino acid residues independently are any non-proteinogenic or proteinogenic alpha-amino acid residue of the general formula VI



formula VI

wherein Q^5 is $-CH_2-$ or -CO-,

l^5, q^5 and r^5 are independently 0, 1, 2, 3, 4, 5, or 6,

X^5 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

Y^5 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^5 or Z^5,

Z^5 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond;

or the residues of any of the following, non-proteinogenic amino acids (R- and S-isomer for chiral amino acids) dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, 3-amino-1,2,4-triazole-5-carboxylic acid, 1,2,3,4-tetrahyroisoquinoline-3-carboxylic acid, amino-biphenylcarboxylic acids, pipecolic acid, nipecotinic acid, isonipecotinic acid, statine, 4-amino-3-hydroxybutyric acid, aminohexanoic acid, 2-amino-2-thiazoline-4-carboxylic acid, 1,2,3,4-tetrahyronorharman-3-carboxylic acid, 3-amino-3-methylbenzoic acid, 3-aminomethylbutanoic acid, 5-aminopentanoic acid, 2-amino-thiazoleacetic acid, 2-aminothiopheneacetic acid, cis- and trans 2-amino-cyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid, 4-amino-methylbenzoic acid, aminonaphthoic aicd, aminopenicillanic acid, 3-aminopyrazole-4-carboxylic acid, 2-amino-4-pentenoic acid, 2-aminothiopheneacetic acid, 3-aminobutyric acid, aminolevulinic acid, 8-aminocaprylic acid ;

the total number of amino acid residues of N and M is equal to or less than 17;

x and y are independently 0 or 1;

when the sidechain of an amino acid residue of either M, A, B, C, D, E, F, G, or N contains an amino group, it can optionally be connected to a sidechain of an amino acid residue of M, A, B, C, D, E, F, G, or N containing a carboxylic acid group in order to generate a linkage of the general formula VII

$$-[CO-(CH_2)_p1\ -(aryl)_s1\ -(CH_2)_t1\ -\ NH]_u1\ -$$

formula VII

wherein u^1 and s^1 are independently 0, 1, or 2,

t^1 and p^1 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8;

when a sidechain of an amino acid residue of either M, A, B, C, D, E, F, G, or N contains a mercapto group, it can optionally be connected to a side-chain of an amino acid residue of either M, A, B, C, D, E, F, G, or N containing an amino group in order to generate a linkage of the general formula VIII

$$-(CH_2)_p2-(aryl)_s2-CO-$$

formula VIII

wherein p^2 is 1, 2, 3, 4, or 5,

s^2 is independently 0 or 1;

when a sidechain of an amino acid residue of either M, A, B, C, D, E, F, G, or N contains a mercapto group, it can optionally be connected to the methylene group of a dehydroalanine residue of either M, A, B, C, D, E, F, G, or N in order to generate a thioether linkage;

when the sidechains of two or more amino acid residues of M, A, B, C, D, E, F, G, or N contain a mercapto group, they can optionally be connected in order to generate a disulfide linkage;

K is $W^1-(CH_2)_v1-CO-$, or $W^2-(CH_2)_v2-NH-CO-$, or $W^3-(CH_2)_v3-O-CO-$, or $W^4-(CH_2)_v4-SO_2-$,

wherein v^1, v^2, v^3 and v^4 independently are 0, 1, 2, 3, 4, 5, or 6,

W^1, W^2, W^3 and W^4 independently are hydrogen, or a hydroxy, C_{1-6}-alkyl, aryl, amino group;

or a linkage to a sidechain of an amino acid residue of M, A, B, C, D, E, F, G, or N containing a carboxylic acid group of the general formula IX

$$- [CO-(CH_2)_p3-(aryl)_s3- (CH_2)_t3- NH]_u3 -$$

formula IX

wherein u^3 and s^3 are independently 0, 1, or 2,

t^3 and p^3 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8;

or a linkage joining K and L of the general formula X

$$- [CO-(CH_2)_p4 -(aryl)_s4 - (CH_2)_t4 - NH]_u4 -$$

formula X

wherein u^4 and s^4 are independently 0, 1, or 2,

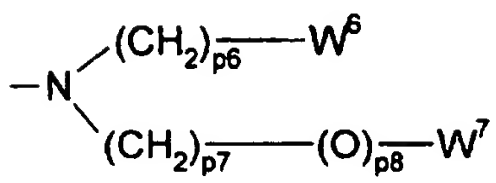
t^4 and p^4 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8;

L is $-O-(CH_2)_p5 -W^6$,

wherein p^5 is 0, 1, 2, 3, 4, 5, or 6,

W^5 is hydrogen, or a hydroxy, C_{1-6}-alkyl, aryl, amino group;

or L is



wherein p^6 and p^7 are independently 0, 1, 2, 3, 4, 5, or 6,

p^8 is 0 or 1,

W^6 and W^7 are independently hydrogen, or a hydroxy, C_{1-6}-alkyl, aryl, amino group, or a valence bond;

or a linkage to an amino group in the sidechain of an amino acid residue of M, A, B, C, D, E, F, G, or N of the general formula XI

$$- [CO-(CH_2)_p9 -(aryl)_s9 - (CH_2)_t9 - NH]_u9 -$$

formula XI

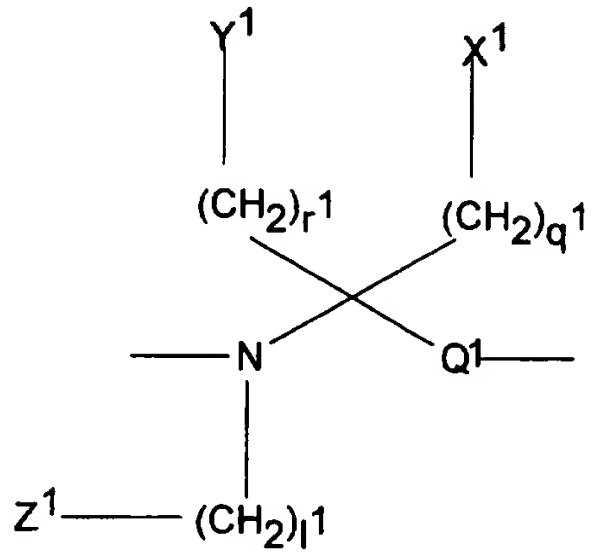
wherein u^9 and s^9 are independently 0, 1 or 2,

t^9 and p^9 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8;

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of formula (I), A is a non-proteinogenic or

proteinogenic amino acid of the general formula II



formula II

wherein Q^1 is $-CH_2-$ or -CO-,

l^1 and r^1 are 0 , q^1 is 0, 1, 2, 3, or 4,

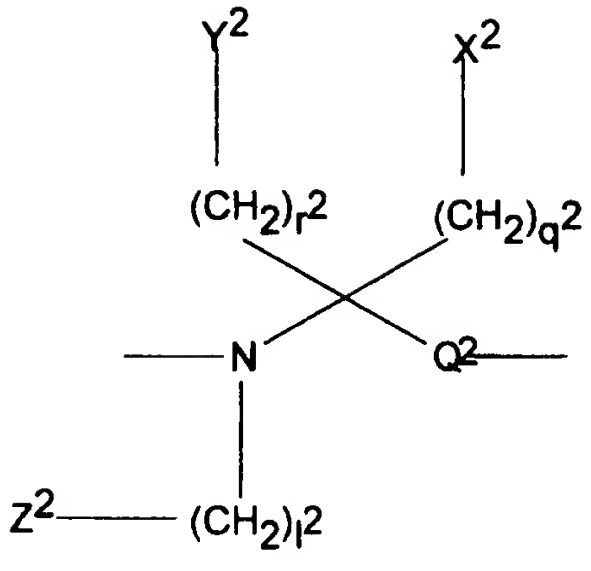
X^1 is hydrogen, isopropyl, tert. butyl, phenyl, cyclopropyl, cyclohexyl, 2-hydroxyethyl, or amino,

Y^1 is hydrogen, or methyl, and

Z^1 is hydrogen;

preferably A is the residue of leucine, isoleucine, valine, phenylalanine, cyclohexylalanine or homophenylalanine, more preferably leucine.

In another embodiment of the compound of formula (I), B is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is -CH_2- or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

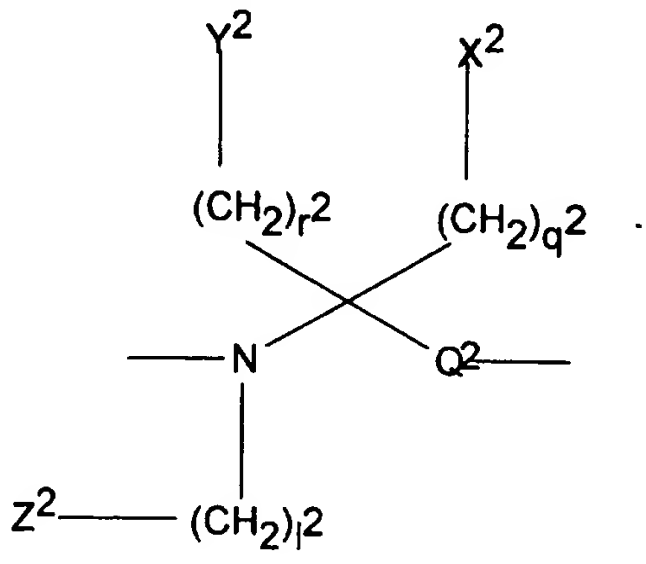
X^2 is hydrogen, phenyl, amino, guanidino, hydroxy, isopropyl, carboxy

Y^2 is hydrogen, or methyl,

Z^2 is hydrogen,
or the residue of any of the following, non-proteinogenic amino acids; dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, cis- and trans 2-aminocyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid or 4-aminomethylbenzoic acid;

preferably B is the residue of glycine, alanine, serine, lysine, ornithine, arginine, glutamic acid or aspartic acid, more preferably alanine.

In a further embodiment of the compound of formula (I), C is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

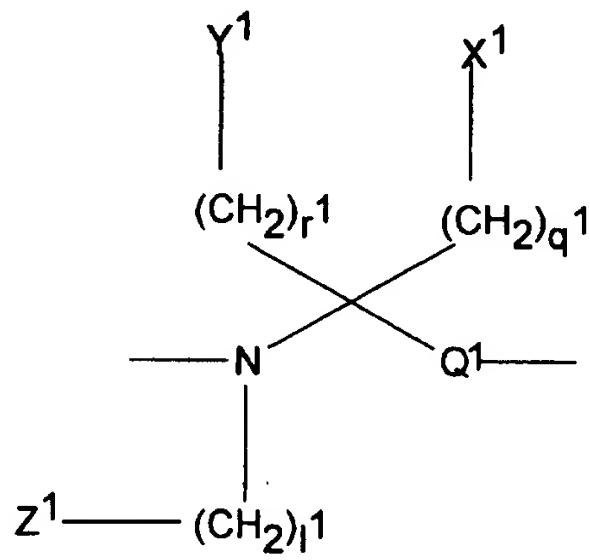
X^2 is hydrogen, imidazolyl, phenyl, amino, hydroxy, isopropyl, carboxy, aminocarbonyl, or guanidino,

Y^2 is hydrogen or methyl,

Z^2 is hydrogen;

preferably C is the residue of lysine, glutamine, glutamic acid, asparagine, aspartic acid, arginine, ornithine, serine or histidine, more preferably glutamine or ornithine.

In a further embodiment of the compound of formula (I), D is a non-proteinogenic or proteinogenic amino acid of the general formula II



formula II

wherein Q^1 is $-CH_2-$ or -CO-,

l^1 and r^1 are 0 , q^1 is 0, 1, 2, 3, or 4,

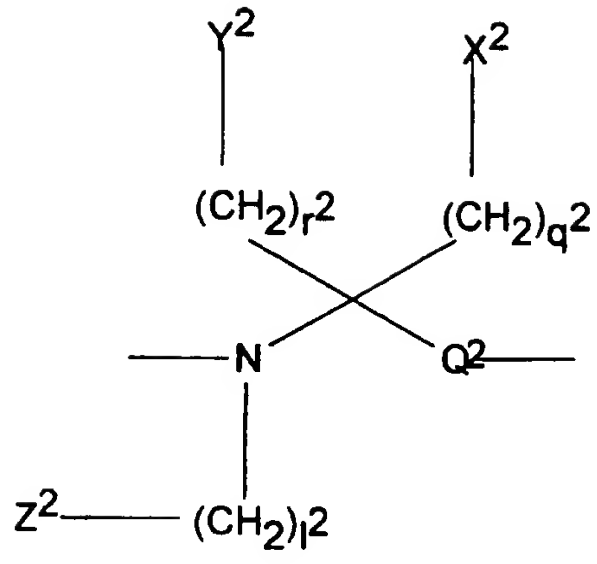
X^1 is hydrogen, isopropyl, tert. butyl, phenyl, cyclopropyl, cyclohexyl, 2-hydroxyethyl, or amino,

Y^1 is hydrogen, or methyl,

Z^1 is hydrogen;

preferably D is the residue of leucine, isoleucine, valine, phenylalanine, cyclohexylalanine or homophenylalanine, more preferably leucine.

In a further embodiment of the compound of formula (I), E is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

X^2 is hydrogen, phenyl, amino, guanidino, hydroxy, isopropyl, carboxy,

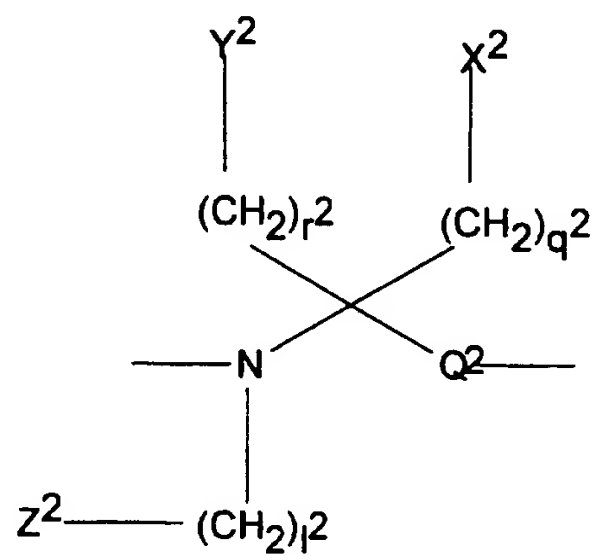
Y^2 is hydrogen, or methyl,

Z^2 is hydrogen,

or the residue of any of the following, non-proteinogenic amino acids; dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, cis- and trans 2-aminocyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid or 4-aminomethylbenzoic acid;

preferably E is the residue of glycine, alanine, serine, threonine, tyrosine, lysine, ornithine, glutamic acid, aspartic acid, homoarginine or arginine, more preferably serine.

In a further embodiment of the compound of formula (I), F is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

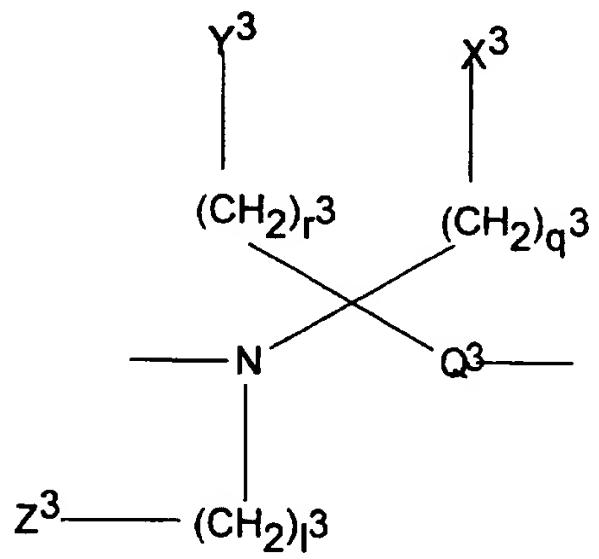
X^2 is hydrogen, phenyl, amino, hydroxy, isopropyl, carboxy, aminocarbonyl,or guanidino,

Y^2 is hydrogen or methyl,

Z^2 is hydrogen;

preferably F is the residue of alanine, phenylalanine, glycine, serine, valine, lysine, glutamine, glutamic acid, asparagine, aspartic acid or arginine, more preferably alanine.

In a further embodiment of the compound of formula (I), G is a non-proteinogenic or proteinogenic amino acid residue of the general formula IV



Formula IV

wherein Q^3 is $-CH_2-$ or -CO-,

l^3 and r^3 are 0, q^2 is 0, 1, 2, 3, or 4,

X^2 is amino, methylamino, dimethylamino, amidino, benzamidino, guanidino, imidazolyl, hydroxy, aminocarbonyl,

Y^2 is hydrogen or methyl,

Z^2 is hydrogen;

preferably G is the residue of arginine, lysine, glutamine, ornithine, histidine, serine or asparagine, more preferably arginine.

In a further embodiment of the compound of formula (I), M is the residue of valine, isoleucine, leucine, penicillamine, lysine, glutamic acid, glutamine, aspartic acid,

arginine, alanine, cysteine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a dipeptide residue and the amino acid residue in the aminoterminal position of the dipeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, aspartic acid or ornithine, the amino acid residue in the second position of the dipeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a tripeptide residue and the amino acid residue in the aminoterminal position of the tripeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidino-phenylalanine or asparagine, preferably arginine, the amino acid residue in the second position of the tripeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the third position of the dipeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a tetrapeptide residue and the amino acid residue in the aminoterminal position of the tetrapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine,

glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the second position of the tetrapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the third position of the tetrapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the fourth position of the tetrapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a pentapeptide residue and the amino acid residue in the aminoterminal position of the pentapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the second position of the pentapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the third position of the pentapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the fourth position of the pentapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the fifth position of the pentapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine,

methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a hexapeptide residue and the amino acid residue in the aminoterminal position of the hexapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the second position of the hexapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the third position of the hexapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthyl-alanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the fourth position of the hexapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidino-phenylalanine or asparagine, preferably arginine, the amino acid residue in the fifth position of the hexapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the sixth position of the hexapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a heptapeptide residue and the amino acid residue in the aminoterminal position of the heptapeptide is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the second position of the

heptapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the third position of the heptapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the fourth position of the heptapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the fifth position of the heptapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the sixth position of the heptapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the seventh position of the heptapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is an octapeptide residue and the amino acid residue in the aminoterminal position of the octapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the second position of the octapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the third position of the octapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine,

lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the fourth position of the octapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the fifth position of the octapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the sixth position of the octapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidino-phenylalanine or asparagine, preferably arginine, the amino acid residue in the seventh position of the octapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the eighth position of the octapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a nonapeptide residue and the amino acid residue in the aminoterminal position of the nonapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the second position of the nonapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexyl-alanine or lysine, preferably phenylalanine, the amino acid residue in the third position of the nonapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in

the fourth position of the nonapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the fifth position of the nonapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the sixth position of the nonapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the seventh position of the nonapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the eighth position of the nonapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the ninth position of the nonapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is a decapeptide residue and the amino acid residue in the aminoterminal position of the decapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in the second position of the decapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the third position of the decapeptide residue is the residue of phenylalanine, tyrosine, tryptophane,

histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the fourth position of the decapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the fifth position of the decapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the sixth position of the decapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the seventh position of the decapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the eighth position of the decapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-amino-phenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the ninth position of the decapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the tenth position of the decapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is an undecapeptide residue and the amino acid residue in the aminoterminal position of the undecapeptide residue is the residue of asparagine, glutamine, serine, aspartic acid, glutamic acid, lysine, alanine, threonine, methionine, arginine, histidine or

leucine, preferably aspartic acid, the amino acid residue in the second position of the undecapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in the third position of the undecapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the fourth position of the undecapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexyl-alanine or lysine, preferably phenylalanine, the amino acid residue in the fifth position of the undecapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the sixth position of the undecapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the seventh position of the undecapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the eighth position of the undecapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenyl-alanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the ninth position of the undecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the tenth position of the undecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the eleventh position of the undecapeptide residue is the residue of valine, isoleucine, leucine,

penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is an dodecapeptide residue and the amino acid residue in the aminoterminal position of the dodecapeptide residue is the residue of alanine, valine, leucine, serine, threonine, lysine, cysteine, glutamine, glutamic acid, asparagine, aspartic acid, glycine, N-methylalanine or histidine, preferably alanine or N-methylalanine, the amino acid residue in the second position of the dodecapeptide residue is the residue of asparagine, glutamine, serine, aspartic acid, glutamic acid, lysine, alanine, threonine, methionine, arginine, histidine or leucine, preferably aspartic acid, the amino acid residue in the third position of the dodecapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in the fourth position of the dodecapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the fifth position of the dodecapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthyl-alanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the sixth position of the dodecapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the seventh position of the dodecapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the eighth position of the dodecapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino

acid residue in the ninth position of the dodecapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthyl-alanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the tenth position of the dodecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenyl-alanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the eleventh position of the dodecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the twelvth position of the dodecapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), M is an tredecapeptide residue and the amino acid residue in the aminoterminal position of the tredecapeptide residue is the residue of tyrosine, histidine, phenylalanine, tryptophane, lysine, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, glutamine or asparagine, preferably tyrosine, the amino acid residue in the second position of the tredecapeptide residue is the residue of alanine, valine, leucine, serine, threonine, lysine, cysteine, glutamine, glutamic acid, asparagine, asparticacid, glycine, N-methylalanine or histidine, preferably alanine or N-methyl-alanine, the amino acid residue in the third position of the tredecapeptide residue is the residue of asparagine, glutamine, serine, aspartic acid, glutamic acid, lysine, alanine, threonine, methionine, arginine, histidine or leucine, preferably aspartic acid, the amino acid residue in the fourth position of the tredecapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in

the fifth position of the tredecapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the sixth position of the tredecapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the seventh position of the tredecapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the eighth position of the tredecapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the ninth position of the tredecapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the tenth position of the tredecapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the eleventh position of the tredecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the twelvth position of the tredecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the thirteenth position of the tredecapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

In a further embodiment of the compound of formula (I), N is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine.

In a further embodiment of the compound of formula (I), N is a dipeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the carboxyterminal position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine.

In a further embodiment of the compound of formula (I), N is a tripeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the carboxyterminal position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine.

In a further embodiment of the compound of formula (I), N is a tetrapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine,

alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the carboxyterminal position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine.

In a further embodiment of the compound of formula (I), N is a pentapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the carboxyterminal position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine.

In a further embodiment of the compound of formula (I), N is a hexapeptide residue

and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the carboxyterminal position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine.

In a further embodiment of the compound of formula (I), N is a heptapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine,

glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine, the amino acid residue in the carboxyterminal position is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine.

In a further embodiment of the compound of formula (I), N is an octapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or

alanine, the amino acid residue in the seventh position is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine, the amino acid residue in the carboxyterminal position is the residue of serine, threonine, alanine, cysteine, asparagine, aspartic acid, glutamic acid, glutamine, histidine, arginine, tyrosine or homocysteine.

In a further embodiment of the compound of formula (I), N is a nonapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine, the amino acid residue in the seventh position is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine, the amino acid residue in the eighth position is the residue of serine, threonine, alanine, cysteine, asparagine,

aspartic acid, glutamic acid, glutamine, histidine, arginine, tyrosine or homocysteine, the amino acid residue in the carboxyterminal position is the residue of arginine, lysine, ornithine, histidine, glutamine, glutamic acid, asparagine, aspartic acid, serine, tyrosine, homocysteine or alanine.

In a further embodiment of the compound of formula (I), N is a decapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine, the amino acid residue in the seventh position is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine, the amino acid residue in the eighth position is the residue of serine, threonine, alanine, cysteine, asparagine, aspartic acid, glutamic acid, glutamine, histidine, arginine, tyrosine or homocysteine, the amino acid residue in the ninth position is the residue of

arginine, lysine, ornithine, histidine, glutamine, glutamic acid, asparagine, aspartic acid, serine, tyrosine, homocysteine or alanine, the amino acid residue in the carboxyterminal position is the residue of glutamine, glutamic acid, histidine, lysine, asparagine, aspartic acid, arginine, serine, threonine or tyrosine.

In a further embodiment of the compound of formula (I), K is hydrogen or a group of formula W^1-$(CH_2)_{v1}$-CO-, wherein W^1 is hydrogen, hydroxy or C_{1-6}-alkyl, preferably hydrogen, and v^1 is 0, 1, 2, 3 or 4, preferably 1.

In a further embodiment of the compound of formula (I), L is

wherein p^6 and p^7 independently are 0, 1 or 2, preferably 0; W^6 is hydrogen, hydroxy or C_{1-6}-alkyl, preferably hydrogen; p^8 is 0 or 1, preferably 0; W^7 is hydrogen, hydroxy or C_{1-6}-alkyl, preferably hydrogen.

All of the above embodiments are independent of each other.

Preferred compounds of the invention are:

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2,

Asp-Ala-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2,

Asp-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2,

Asp-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Cyclo(Glu^9-Lys^{13})-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Lys-His-NH_2,

Cyclo(Lys^5-Glu^9)-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Tyr-Arg-Lys-Val-Leu-Glu-Gln-Leu-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Phe-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Phe-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Tyr-Ala-Arg-His-NH_2,

Asp-Ala-Gln-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Glu-Val-Leu-Arg-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Cyclo(Asp^1-[Gly]-Orn^5)-Asp-Ala-Tyr-Arg-Orn-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Lys-His-NH_2,

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Lys-His-NH_2,

Cyclo(Lys^2-Glu^6)-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Cyclo(Lys^4-Glu^8)-Lys-Val-Leu-Lys-Gln-Leu-Ser-Glu-Arg-NH_2,

Cyclo(Orn^2-[$COCH_2$]-Pen^6)-(Asp-Orn-Tyr-Arg-Lys-Pen-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-NH_2,

Cyclo(Lys^3-Glu^7)-Lys-Val-Leu-Lys-Gln-Leu-Ser-Glu-Arg-His-NH_2

Cyclo(Lys^2-Glu^6)-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys^3-Glu^7)-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Glu[1]-Lys[5])-Glu-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys[4]-Glu[8])-Asp-Ala-Tyr-Lys-Lys-Val-Leu-Glu-Gln-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys[3]-Glu[7])-Ala-Tyr-Lys-Lys-Val-Leu-Glu-Gln-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys[4]-Glu[8])-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-NH_2,

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Ac-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp[2]-[gly]-Orn[6])-Ac-Asp-Asp-Ile-Phe-Thr-Orn-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp[6]-[gly]-Orn[10])-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Orn-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp[10]-[gly]-Orn[14])-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Asp-Val-Leu-Ala-Orn-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2, or

Ac-(N-Me)Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2.

Particular preferred compounds of the invention are:

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Ac-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp^2-[gly]-Orn^6)-Ac-Asp-Asp-Ile-Phe-Thr-Orn-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp^6-[gly]-Orn^{10})-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Orn-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp^{10}-[gly]-Orn^{14})-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Asp-Val-Leu-Ala-Orn-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2, or

Ac-(N-Me)Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2.

We have discovered that the rat and human GHRH receptor display different structure activity relations for the human GHRH (hGHRH) peptide. We have designed a series of truncated analogs of hGHRH. The analogs activates the

GHRH receptor, but does not have the disadvantages of GHRH. An advantage of these truncated analogs is their improved metabolic stability. Further the truncated analogs may offer advantages with respect to prolonged or modified duration of action, decreased immunogenicity, selectivity/side effects and lower cost of production.

In the above structural formulas and throughout the present specification, the following terms have the indicated meanings:

The C_{1-6}-alkyl residues specified above are intended to include those alkyl residues of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkyl are methyl, ethyl, propyl, butyl, pentyl, and hexyl. Examples of branched alkyl are isopropyl, sec-butyl, tert-butyl, isopentyl, and isohexyl. Examples of cyclic alkyl are C_{3-6}-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The C_{1-6}-alkoxy residues specified above are intended to include those alkoxy residues of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkyloxy are methoxy, ethoxy, propoxy, butoxy, pentoxy, and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

In the present context, the term "aryl" is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected from the group consisting of phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl.

Aryl is preferably phenyl, thienyl, imidazolyl, pyridyl, indolyl, oxadiazole, quinoline or naphthyl.

The term "halogen" is intended to include chlorine (Cl), fluorine (F), bromine (Br) and iodine (I).

Certain of the above defined terms may occur more than once in the above formula I, and upon such occurence each term shall be defined independently of the other.

The compounds of the present invention may have one or more asymmetric centres and it is intended that stereoisomers, as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention.

The compounds of the present invention may optionally be on a pharmaceutically acceptable salt form such as the pharmaceutically acceptable acid addition salts of compounds of formula I which include those prepared by reacting the compound of formula I with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, acetic, phosphoric, lactic, maleic, phthalic, citric, glutaric, gluconic, methanesulfonic, salicylic, succinic, tartaric, toluenesulfonic, trifluoracetic, sulfamic or fumaric acid.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form or, where appropriate, as a alkali metal or alkaline earth metal or lower alkylammonium salt. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

In another aspect, the present invention relates to a pharmaceutical composition comprising, as an active ingredient, a compound of the general formula I or a

pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington's Pharmaceutical Sciences, 1985. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

The pharmaceutical carrier or diluent employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water.

Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	100mg
Colloidal silicon dioxide (Aerosil)	1.5mg
Cellulose, microcryst. (Avicel)	70mg
Modified cellulose gum (Ac-Di-Sol)	7.5mg
Magnesium stearate	
Coating:	
HPMC approx.	9mg
*Mywacett 9-40 T approx.	0.9mg

*Acylated monoglyceride used as plasticizer for film coating.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising 50-200 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is suitably 0.1-500 mg/day, e.g. from about 5 to about 50 mg, such as about 10 mg per dose, when administered to patients, e.g. humans, as a drug.

It has been demonstrated that compounds of the general formula I possess the ability to release endogenous growth hormone *in vivo*. The compounds may

therefore be used in the treatment of conditions which require increased plasma growth hormone levels such as in growth hormone deficient humans or in elderly patients or livestock.

Thus, in a particular aspect, the present invention relates to a pharmaceutical composition for stimulating the release of growth hormone from the pituitary, the composition comprising, as an active ingredient, a compound of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

In a further aspect, the present invention relates to a method of stimulating the release of growth hormone from the pituitary, the method comprising administering to a subject in need thereof an effective amount of a compound of the general formula I or a pharmaceutically acceptable salt thereof.

In a still further aspect, the present invention relates to the use of a compound of the general formula I or a pharmaceutically acceptable salt thereof for the preparation of a medicament for stimulating the release of growth hormone from the pituitary.

To those skilled in the art, it is well known that the current and potential uses of growth hormone in humans are varied and multitudinous. Thus, compounds of formula I can be administered for purposes stimulating release of growth hormone from the pituitary and would then have similar effects or uses as growth hormone itself. The uses of growth hormone may be summarized as follows: stimulation of growth hormone release in the elderly; prevention of catabolic side effects of glucocorticoids, prevention and treatment of osteoporosis, stimulation of the immune system, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting from

growth retardation, treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with the Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients, treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound healing and psychosocial deprivation, treatment of pulmonary dysfunction and ventilator dependency, attenuation of protein catabolic responses after major surgery, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis, adjuvant treatment for ovulation induction; to stimulate thymic development and prevent the age-related decline of thymic function, treatment of immunosuppressed patients, improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly, stimulation of osteoblasts, bone remodelling and cartilage growth, stimulation of the immune system in companion animals and treatment of disorder of aging in companion animals, growth promoter in livestock and stimulation of wool growth in sheep.

For the above indications the dosage will vary depending on the compound of formula I employed, on the mode of administration and on the therapy desired. However, generally dosage levels between 0.0001 and 100 mg/kg body weight daily are administered to patients and animals to obtain effective release of endogenous growth hormone. Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.0001 mg to about 100 mg, preferably from about 0.001 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more compounds exhibiting a different activity, e.g., an antibiotic or other pharmacologically active material.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral, the oral route being preferred.

Apart from the pharmaceutical use of the growth hormone releasing hormones of formula I, they may be useful in vitro tools for investigating the regulation of growth hormone release.

The compounds of Formula I are also useful in vivo tools for evaluating the growth hormone releasing capability of the pituitary. For example, serum samples taken before and after administration of these compounds to humans can be assayed for growth hormone. Comparison of the growth hormone in each serum sample would directly determine the ability of the patients pituitary to release growth hormone.

The compounds of Formula I can be administered to commercially important animals to increase their rate and extent of growth, and to increase milk production.

Accordingly, the present invention include within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the pharmaceutical composition can comprise at least one of the compounds of Formula I combined with compounds exhibiting a different activity, e.g., an antibiotic or other pharmacologically active material.

A further use of the compounds of Formula I is in combination with other secretagogues like GHRP's, such as GHRP (2 or 6), growth hormone and its analogues or somatomedins including IGF-1 and IGF-2.

For the above indications, dosage will vary depending on the compound of Formula I employed, on the mode of administration and on the therapy desired. However, generally dose levels between 0.0001 to 100 mg/kg body weight daily are administered to patients and animals to obtain effective release of endogenous growth hormone.

The route of administration may be any route which affectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral, the oral route being the preferred.

Any novel feature or combination of features described herein is considered essential to this invention.

Pharmacological Methods

Examples:

Compounds of Formula I were evaluated in vitro for their efficacy and potency to stimulate the human GHRH receptor in cell lines stably expressing this receptor. Briefly, 80 % confluent cells were scraped off and pelleted at 10,000xg for 10 min at 4°C.

1.

For binding assay the cell pellet was homogenized in 10 mM Tris-acetate buffer (pH 7.4) and centrifuged at 50,000xg for 10 min at 4C. The pellet were

rehomogenized in the same buffer and diluted to 200 ug membrane protein/ml. Assay consisted of 25 ul ^{125}I-GHRH(1-29)NH_2 (200,000cpm/tube), 900 ul Tris-acetate buffer and 25 ul 0.2 % Tween 20. This mixture was incubated for 45 min at room temperature. The reaction was terminated by rapid filtration through GF/B filters pre-wetted with 0.5 % PEI.

2.

For Adenylyl cyclase assay the cell pellet was processed and assay performed as described previously for Dopamine D1 receptors in Pedersen et al., Eur. J. Pharmacol. 267, 85-93, 1994.

3.

Compounds of Formula I were evaluated in vitro for their efficacy and potency to release growth hormone in primary rat somatotrophs. Rat primary somatotrophs were prepared essentially as described previously (Chen et al., Endocrinology 129, 3337-3342, 1991 and Chen et al., Endocrinology, 124, 2791-2798, 1989). Briefly, rats were killed by decapitation. The pituitary were quickly removed. The pituitaries were digested with 0.2 % collagenase n 0.2% hyaluronidase in Hanks balanced salt solution. The cells were resuspended in Dulbecco@s modified eagles medium containing 0.37 % $NaHCO_2$, 10 % horse serum, 2.5 % fetal calf serum, 1 % nonessential amino acids, 1 % glutamine and 1 % pen/strep and adjusted to $1.5x10^5$ cells/ ml. One ml of this suspension was placed in each well of 24-well trays and left for 2-3 days before release experiments were performed.

On the day of the experiments, cells were washed twice with the above medium containing 25 mM HEPES, pH 7.4. Growth hormone release were initiated by addition of medium containing 25 mM HEPES and test compound. Incubation was carried out for 15 min at 37°C. After incubation growth hormone released to the medium was measured by a standard RIA assay.

EXAMPLES:

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which however, are not to be construed as limiting.

The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts (d) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in ^{0}C. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

Abbrevations:

TLC:	thin layer chromatography
DMSO:	dimethylsulfoxide
min:	minutes
h:	hours

Experimental Procedures:

Method 1:

Linear peptides were synthesized with an ABI 431A peptide synthesizer using

standard protocols according to the Fmoc SPPS strategy (as substantially described by Fields et al., Int. J. Pept. Protein Res. **35**, *1990*, 161) on Rink amide polystyrene resin [4-((4',2'-dimethoxyphenyl)-(Fmoc-amino)methyl)-phenoxy resin, e.g. Novabiochem, Bad Soden, Germany, cat.# 01-64-0013]. The peptides were cleaved from resin using standard cleavage cocktails containing a mixture of trifluoroactic acid and common scavengers (e.g., a mixture of trifluoroacetic acid (4 mL), phenol (300 mg), ethanedithiol (0.10 mL), thioanisole (0.20 mL) and water (0.20 mL), or as substantially described in the "novabiochem catalog and Peptide Synthesis Handbook" 94/95 on pages S34 to S36 and in references 1 to 15 listed on page S39). Subsequently, the cleavage mixture was concentrated to 1 mL using a stream of nitrogen, and the crude peptides were precipitated from this oil with diethyl ether (45 mL), washed with diethyl ether (3 portions of 50 mL) and dried.

Purifications were performed by semipreparative HPLC using a Sep-Pak C18 cartridge (Waters part.# 51910). All purified peptides were characterized by at least one analytical HPLC chromatogram on a Waters 510 system equipped with a Vydac C18 column (5 to 60% acetonitrile in water, 42°C, 0.1 M ammonium sulfate, pH adjusted to 2.5 with 4 M sulfuric acid, 50 min) and plasma desorption mass spectroscopy.

The following peptides were prepared by method 1 (retention time R_t using a gradient of 5 to 60% acetonitrile in water, 42°C, 0.1 M ammonium sulfate, pH adjusted to 2.5 with 4 M sulfuric acid, 50 min; calculated molecular mass, found molecular mass):

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 [R_t= 20.98 min]

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2 [R_t= 21.93 min]

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 [R_t = 23.75 min; calculated 1669.0, found 1669±2

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2 [R_t = 24.37 min; calculated 1670.0, found 1669.2±2

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Lys-His-NH_2 [R_t = 22.85 min; calculated 1642.0, found1640.7±2

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 29.33 min, M = 2408 ± 1)

Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2 (R_t = 31.98 min, M = 2701 ± 3),

Ac-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2 (R_t = 32.33 min, M = 2771 ± 3)

Ac-(N-Me)Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2 (R_t = 32.78 min, M = 2784 ± 3)

Method 2:

Linear peptides were synthesized using standard protocols according to the Fmoc SPPS strategy (as substantially described by Fields et al., Int. J. Pept. Protein Res. **35**, *1990*, 161) and to method 1 on either an Abimed 422 MPS, Milligen 9050 continuous flow, or ACT Model 90 2 vessel machine. The peptides were cleaved

from resin using standard cleavage cocktails containing a mixture of trifluoroactic acid and common scavengers (similar to method 1, or as substantially described in the "novabiochem catalog and Peptide Synthesis Handbook" 94/95 on pages S34 to S36 and in references 1 to 15 listed on page S39). Subsequently, the cleavage mixture was concentrated, and the crude peptides were precipitated with diethyl ether and dried, similar to method 1.

Purifications were performed on a Gilson computer controlled HPLC or EM science 2 liter / min HPLC using a 15 x 50 cm Sep-tech column. All purified peptides were characterized by at least one analytical HPLC chromatogram (5 to 50% acetonitrile in water, 0.1% trifluoroacetic acid, 16 min) and laser desorption mass spectroscopy.

The following peptides were prepared by method 2 (retention time R_t using a gradient of 5 to 50% acetonitrile in water, 0.1% trifluoroacetic acid, 16 min; molecular mass M+H of the singly protonated molecule):

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 9.13 min; M+H = 1624)

Asp-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 10.66 min; M+H = 1556)

Asp-Ala-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 10.84 min; M+H = 1569)

Asp-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 8.47 min; M+H = 1108)

Asp-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 8.03 min; M+H = 1237)

Asp-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 8.12 min; M+H = 1553)

Asp-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 5.92 min; M+H = 1009)

Asp-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 8.07 min; M+H = 1391)

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2 (R_t = 9.07 min; M+H = 1481)

Asp-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2 (R_t = 9.55 min; M+H = 1352)

Asp-Ala-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2 (R_t = 9.70 min; M+H = 1423)

Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 11.77 min; M+H = 2436)

Method 3:

Cyclic peptides by sidechain to sidechain cyclization from an amino to a carboxy group were synthesized using 4-methylbenzhydryl (MBHA) polystyrene resin and an ABI 430 peptide synthesizer employing standard protocols according to the Boc SPPS strategy (e.g, as substantially described by Stewart and Young, Solid Phase Peptide Synthesis, 2nd ed., Rockford, Illinois, USA, 1976). In general, sidechain functionalities intended for cyclization were protected using a base-labile protecting group (Fmoc-protection for amino groups, fluorenylmethylester-protection for

carboxy groups, as described in T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd ed., J. Wiley & Sons, New York 1991, or in the "novabiochem catalog and Peptide Synthesis Handbook" 94/95 on pages S29 to S33 and in references 1 to 16 listed on page S33); other sidechain functionalities were protected using standard, hydrofluoric acid labile protecting groups suitable for Boc peptide synthesis (e.g., as described by Stewart and Young, Solid Phase Peptide Synthesis, 2nd ed., Rockford, Illinois, USA, 1976). For cyclization of peptides via the sidechain functionality of lysine or ornithine, the amino group in the sidechain can be acylated with an Fmoc protected spacer amino acid (e.g., FmocGly); subsequently, the amino group of the spacer amino acid can be used for formation of the amide bond with the sidechain functionality of glutamic acid or aspartic acid. After formation of the cyclic structure and removal of the N-terminal Boc group, further synthesis and final cleavage are carried out under standard conditions for Boc SPPS strategy.

The crude peptide was dried and purified by HPLC on a 20 mm x 250 mm column packed with 7 µ C-18 silica which was preequilibrated with 15% CH_3CN in 0.05 M $(NH_4)_2SO_4$, which was adjusted to pH 2.5 with 4 M H_2SO_4. The crude peptide was dissolved in 2 mL 70% CH_3CN / 0.1% TFA in H_2O and diluted to 100 mL with H_2O. This solution was divided into two equal portions and each of them were injected on the column in two separate runs. The column was eluted with a gradient of 15% - 25% CH_3CN in 0.05 M $(NH_4)_2SO_4$, pH 2.5 at 10 mL/min during 47 min at 40°C. The peptide-containing fractions were collected, diluted with 3 volumes of H_2O and applied to a Sep-Pak® C18 cartrtidge (Waters part. #:51910) which was equilibrated with 0.1% TFA / H_2O. The peptide was eluted from the Sep-Pak® cartridge with 70% CH_3CN / 0.1% TFA / H_2O and isolated from the eluate after dilution with water.

The final product obtained was characterized by analytical RP-HPLC (retention time) and by plasma desorption mass spectrometry (molecular mass). Mass spectrometry

ageed with the expected structure within the experimental error of the method.

The RP-HPLC analysis was performed using UV-detection at 214 nm and a Vydac 218TP54 4.6 mm x 250 mm 5µ C-18 silica column (the Separations Group, Hesperia) which was eluted at 1 mL/min at 42 °C. Two different elution conditions were used:

A1: The column was equilibrated with 5% CH_3CN in a buffer consisting of 0.1 M $(NH_4)_2SO_4$, which was adjusted to pH 2.5 with 4 M H_2SO_4 , and eluted with a gradient of 5% to 60% CH_3CN in the same buffer during 50 min.

B1: The column was equilibrated with 5% CH_3CN / 0.1% TFA / H_2O and eluted by a gradient of 5% CH_3CN / 0.1% TFA / H_2O to 60 % CH_3CN / 0.1% TFA / H_2O during 50 min.

Cyclo (Asp^2-[Gly]-Orn^6)-Ac-Asp-Asp-Ile-Phe-Thr-Orn-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2 (R_t A1 = 33.11 min, R_t B1 = 34.65 min, M = 2781 ± 3)

Cyclo (Asp^6-[Gly]-Orn^{10})-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Orn-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2 (R_t A1 = 34.30 min, R_t B1 = 36.28 min, M = 2723 ± 3)

Cyclo (Asp^{10}-[Gly]-Orn^{14})-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Asp-Val-Leu-Ala-Orn-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2 (R_t A1 = 33.90 min, R_t B1 = 35.72 min, M = 2710 ± 3)

Cyclo(Asp^1-[Gly]-Orn^5)-Asp-Ala-Tyr-Arg-Orn-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2 (R_t = 23.17 min; M = 1652)

Abbreviations and definitions: Pen = penicillamine, Orn = ornithine, Nleu = Norleucine, homoarg = homoarginine, SPPS = solid phase peptide synthesis, Fmoc = fluorenylmethoxycarbonyl; Boc = tert.butyloxycarbonyl

Cyclo(Glu^9-Lys^{13}) means that the sidechains of Glu^9 and Lys^{13} are connected by an amide bond under formation of a cyclic structure;

Cyclo(Lys^5-Glu^9) means that the sidechains of Lys^5 and Glu^9 are connected by an amide bond under formation of a cyclic structure;

Cyclo(Asp^1-[Gly]-Orn^5) means that the sidechain of Asp^1 is connected by an amide bond to the amino group of Gly by an amide bond and that the carboxylate of Gly is connected by an amide bond to the amino group of Orn^5 under formation of a cyclic structure;

Cyclo(Asp^2-[Gly]-Orn^6) means that the sidechain of Asp^2 is connected by an amide bond to the amino group of Gly by an amide bond and that the carboxylate of Gly is connected by an amide bond to the amino group of Orn^6 under formation of a cyclic structure;

Cyclo(Asp^6-[Gly]-Orn^{10}) means that the sidechain of Asp^6 is connected by an amide bond to the amino group of Gly by an amide bond and that the carboxylate of Gly is connected by an amide bond to the amino group of Orn^{10} under formation of a cyclic structure;

Cyclo(Asp^{10}-[Gly]-Orn^{14}) means that the sidechain of Asp^{10} is connected by an amide bond to the amino group of Gly by an amide bond and that the carboxylate of Gly is connected by an amide bond to the amino group of Orn^{14} under formation of a cyclic structure;

Cyclo(Lys^4-Glu^8) means that the sidechains of Lys^4 and Glu^8 are connected by an amide bond under formation of a cyclic structure;

Cyclo(Orn^2-[$COCH_2$]-Pen^6) means that the sidechain of Orn^2 is connected by an amide bond to the carboxylate of an acetic acid moiety and that the methylene group of the acetic acid moiety is connected by a thioether bond to the sulfur atom

of Pen^6 under formation of a cyclic structure;

Cyclo(Lys^3-Glu^7) means that the sidechains of Lys^3 and Glu^7 are connected by an amide bond under formation of a cyclic structure;

Cyclo(Lys^2-Glu^6) means that the sidechains of Lys^2 and Glu^6 are connected by an amide bond under formation of a cyclic structure;

Cyclo(Glu^1-Lys^5) means that the sidechains of Glu^1 and Lys^5 are connected by an amide bond under formation of a cyclic structure.

CLAIMS:

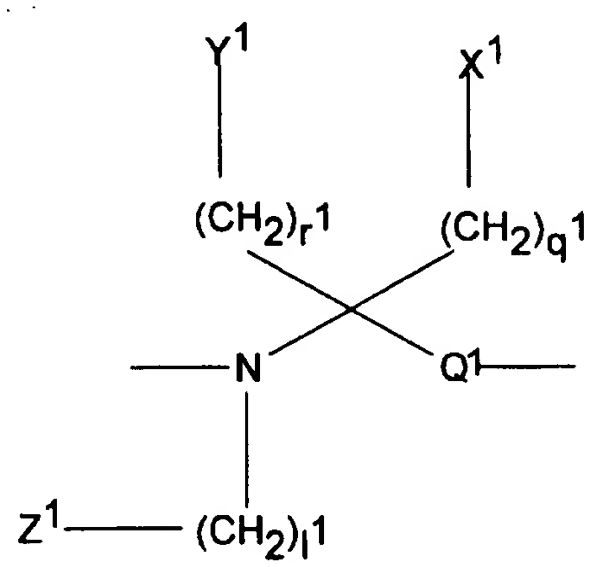
1. A compound of the general formula I

$$K\text{-}(M)_x\text{-}A\text{-}B\text{-}(C)_w\text{-}D\text{-}E\text{-}(F)_z\text{-}G\text{-}(N)_y\text{-}L$$

(I)

wherein z and w are independently 0 or 1,

A and D are independently a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula II



formula II

wherein Q^1 is $-CH_2-$ or -CO-,

l^1 ,q^1 and r^1 are independently 0, 1, 2, 3, 4, 5, or 6,

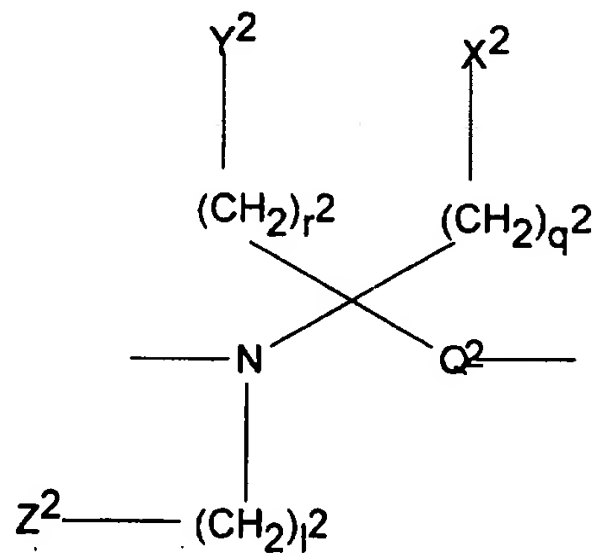
X^1 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group,

or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

Y^1 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^1 or Z^1

Z^1 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

B, C, E, F are independently a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 , q^2 and r^2 are independently 0, 1, 2, 3, 4, 5, or 6,

X^2 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

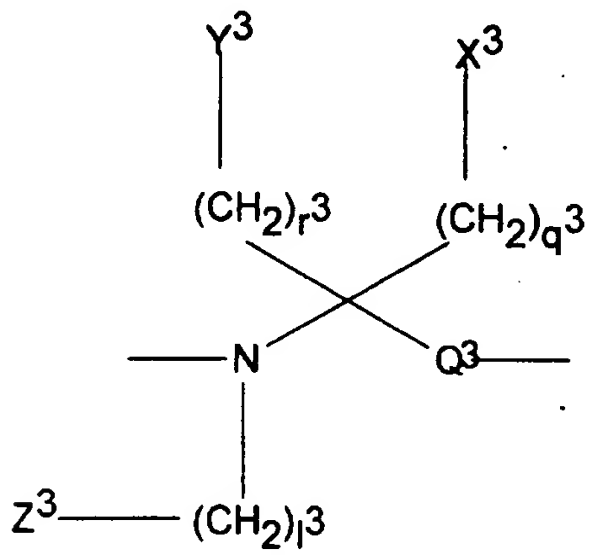
Y^2 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^2 or Z^2,

Z^2 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond;

or the residues of any of the following, non-proteinogenic amino acids (R- and S-isomer for chiral amino acids) dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, 3-amino-1,2,4-triazole-5-carboxylic acid, 1,2,3,4-tetrahyroisoquinoline-3-carboxylic acid, aminobiphenylcarboxylic acids, pipecolic acid, nipecotinic acid, isonipecotinic acid, statine, 4-amino-3-hydroxybutyric acid, aminohexanoic acid, 2-amino-2-thiazoline-4-carboxylic acid, 1,2,3,4-tetrahyronorharman-3-carboxylic acid, 3-amino-3-methylbenzoic acid, 3-aminomethylbutanoic acid, 5-aminopentanoic acid, 2-aminothiazoleacetic acid, 2-aminothiopheneacetic acid, cis- and trans 2-aminocyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid, 4-aminomethylbenzoic acid, aminonaphthoic aicd, aminopenicillanic acid, 3-aminopyrazole-4-carboxylic acid, 2-

amino-4-pentenoic acid, 2-aminothiopheneacetic acid, 3-aminobutyric acid, aminolevulinic acid, 8-aminocaprylic acid ;

G is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula IV



formula IV

wherein Q^3 is $-CH_2-$ or -CO-,

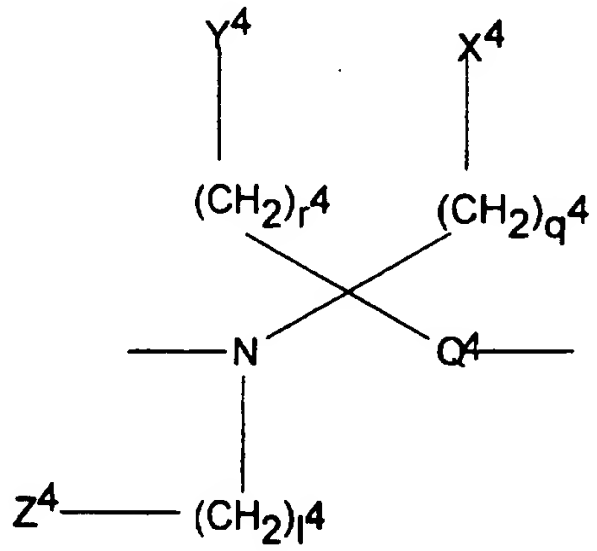
l^3, q^3 and r^3 are independently 0, 1, 2, 3, 4, 5, or 6,

X^3 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

Y^3 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^3 or Z^3,

Z^3 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

M is an amino acid residue, a dipeptide residue, a tripeptide residue, a tetrapeptide residue, a pentapeptide residue, a hexapeptide residue, a heptapeptide residue, a octapeptide residue, a nonapeptide residue, a decapeptide residue, a undecapeptide residue, a dodecapeptide residue or a tredecapeptide residue, wherein the amino acid residues are independently any non-proteinogenic or proteinogenic alpha amino acid residue of the general formula V



formula V

wherein Q^4 is $-CH_2-$ or -CO-,

l^4, q^4 and r^4 are independently 0, 1, 2, 3, 4, 5, or 6,

X^4 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

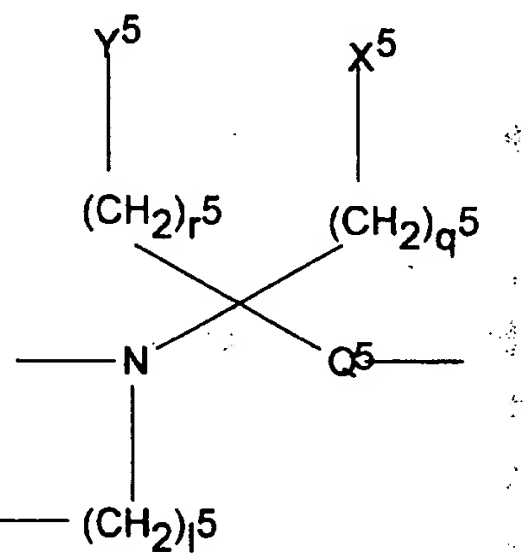
Y^4 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^4 or Z^4,

Z^4 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond;

or the residues of any of the following, non-proteinogenic amino acids (R- and S-isomer for chiral amino acids) dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, 3-amino-1,2,4-triazole-5-carboxylic acid, 1,2,3,4-tetrahyroisoquinoline-3-carboxylic acid, aminobiphenyl-carboxylic acids, pipecolic acid, nipecotinic acid, isonipecotinic acid, statine, 4-amino-3-hydroxybutyric acid, aminohexanoic acid, 2-amino-2-thiazoline-4-carboxylic acid, 1,2,3,4-tetrahyronorharman-3-carboxylic acid, 3-amino-3-methyl-benzoic acid, 3-aminomethylbutanoic acid, 5-aminopentanoic acid, 2-amino-thiazoleacetic acid, 2-aminothiopheneacetic acid, cis- and trans 2-amino-cyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid, 4-amino-methylbenzoic acid, aminonaphthoic aicd, aminopenicillanic acid, 3-aminopyrazole-

4-carboxylic acid, 2-amino-4-pentenoic acid, 2-aminothiopheneacetic acid, 3-aminobutyric acid, aminolevulinic acid, 8-aminocaprylic acid ;

N is an amino acid residue, a dipeptide residue, an oligopeptide residue or an oligoamide residue which is between 1 to 10 amino acid residues long wherein the amino acid residues independently are any non-proteinogenic or proteinogenic alpha-amino acid residue of the general formula VI



formula VI

wherein Q^5 is $-CH_2-$ or -CO-,

l^5, q^5 and r^5 are independently 0, 1, 2, 3, 4, 5, or 6,

X^5 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond,

Y^5 is hydrogen, a C_{1-6}-alkyl group, or a valence bond to X^5 or Z^5,

Z^5 is hydrogen, or a C_{1-6}-alkyl group optionally substituted with a halogen, hydroxy, C_{1-6}-alkoxy, aryloxy, mercapto, C_{1-6}-alkylmercapto, arylmercapto, guanidino, amidino, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, carboxy, carbamoyl, aryl group, or an aryl group optionally substituted with a hydroxy, halogen, mercapto, carboxy, carbamoyl, amino, C_{1-6}-dialkylamino, C_{1-6}-alkylamino, amidino, guanidino, C_{1-6}-alkoxy, C_{1-6}-alkyl group, or a valence bond;

or the residues of any of the following, non-proteinogenic amino acids (R- and S-isomer for chiral amino acids) dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, 3-amino-1,2,4-triazole-5-carboxylic acid, 1,2,3,4-tetrahyroisoquinoline-3-carboxylic acid, aminobiphenyl-carboxylic acids, pipecolic acid, nipecotinic acid, isonipecotinic acid, statine, 4-amino-3-hydroxybutyric acid, aminohexanoic acid, 2-amino-2-thiazoline-4-carboxylic acid, 1,2,3,4-tetrahyronorharman-3-carboxylic acid, 3-amino-3-methyl-benzoic acid, 3-aminomethylbutanoic acid, 5-aminopentanoic acid, 2-amino-thiazoleacetic acid, 2-aminothiopheneacetic acid, cis- and trans 2-amino-cyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid, 4-amino-methylbenzoic acid, aminonaphthoic aicd, aminopenicillanic acid, 3-aminopyrazole-4-carboxylic acid, 2-amino-4-pentenoic acid, 2-aminothiopheneacetic acid, 3-aminobutyric acid, aminolevulinic acid, 8-aminocaprylic acid ;

the total number of amino acid residues of N and M is equal to or less than 17,

x and y are independently 0 or 1;

when the sidechain of an amino acid residue of either M, A, B, C, D, E, F, G, or N

contains an amino group, it can optionally be connected to a sidechain of an amino acid residue of M, A, B, C, D, E, F, G, or N containing a carboxylic acid group in order to generate a linkage of the general formula VII

$$-[CO-(CH_2)_p1\ -(aryl)_s1\ -(CH_2)_t1\ -\ NH]_u1\ -$$

formula VII

wherein u^1 and s^1 are independently 0, 1, or 2,

t^1 and p^1 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8;

when a sidechain of an amino acid residue of either M, A, B, C, D, E, F, G, or N contains a mercapto group, it can optionally be connected to a side-chain of an amino acid residue of either M, A, B, C, D, E, F, G, or N containing an amino group in order to generate a linkage of the general formula VIII

$$-\ (CH_2)_p2\ -(aryl)_s2\ -\ CO\ -$$

formula VIII

wherein p^2 is 1, 2, 3, 4, or 5,

s^2 is independently 0 or 1;

when a sidechain of an amino acid residue of either M, A, B, C, D, E, F, G, or N contains a mercapto group, it can optionally be connected to the methylene group of a dehydroalanine residue of either M, A, B, C, D, E, F, G, or N in order to

generate a thioether linkage;

when the sidechains of two or more amino acid residues of M, A, B, C, D, E, F, G, or N contain a mercapto group, they can optionally be connected in order to generate a disulfide linkage;

K is W^1-$(CH_2)_v1$-CO- , or W^2-$(CH_2)_v2$-NH-CO- , or W^3-$(CH_2)_v3$-O-CO- , or W^4-$(CH_2)_v4$-SO_2- ,

wherein v^1, v^2, v^3 and v^4 independently are 0, 1, 2, 3, 4, 5, or 6,

W^1, W^2, W^3 and W^4 independently are hydrogen, or a hydroxy, C_{1-6}-alkyl, aryl, amino group;

or a linkage to a sidechain of an amino acid residue of M, A, B, C, D, E, F, G, or N containing a carboxylic acid group of the general formula IX

$$- [CO-(CH_2)_p3-(aryl)_s3- (CH_2)_t3- NH]_u3 -$$

formula IX

wherein u^3 and s^3 are independently 0, 1, or 2,

t^3 and p^3 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8;

or a linkage joining K and L of the general formula X

$$- [CO-(CH_2)_p4 -(aryl)_s4 - (CH_2)_t4 - NH]_u4 -$$

formula X

wherein u^4 and s^4 are independently 0, 1, or 2,

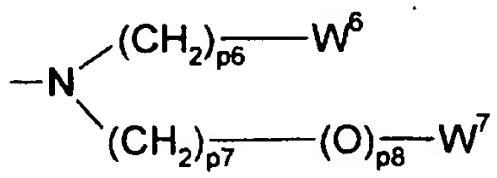
t^4 and p^4 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8;

L is $-O-(CH_2)_p5 -W^5$

wherein p^5 is 0, 1, 2, 3, 4, 5, or 6,

W^5 is hydrogen, or a hydroxy, C_{1-6}-alkyl, aryl, amino group;

or L is



wherein p^6 and p^7 are independently 0, 1, 2, 3, 4, 5, or 6,

p^8 is 0 or 1,

W^6 and W^7 are independently hydrogen, or a hydroxy, C_{1-6}-alkyl, aryl, amino group, or a valence bond;

or a linkage to an amino group in the sidechain of an amino acid residue of M, A, B, C, D, E, F, G, or N of the general formula XI

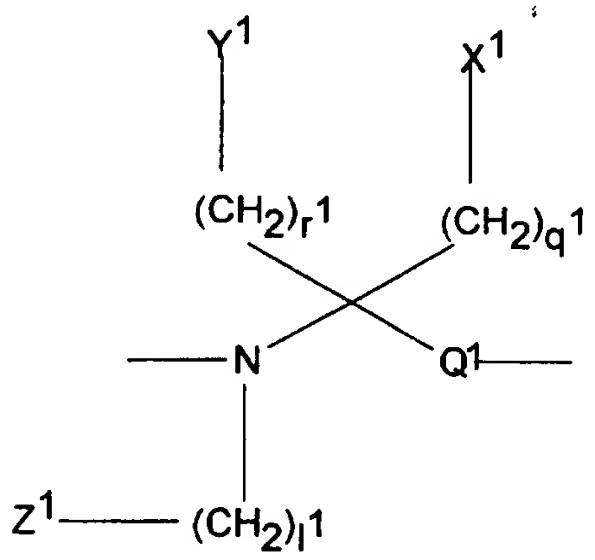
$$- [CO-(CH_2)_p9 -(aryl)_s9 - (CH_2)_t9 - NH]_u9 -$$

formula XI

wherein u^9 and s^9 are independently 0, 1 or 2,

t^9 and p^9 are independently 0, 1, 2, 3, 4, 5, 6, 7, or 8; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein A is a non-proteinogenic or proteinogenic amino acid of the general formula II



formula II

wherein Q^1 is $-CH_2-$ or -CO-,

l^1 and r^1 are 0 , q^1 is 0, 1, 2, 3, or 4,

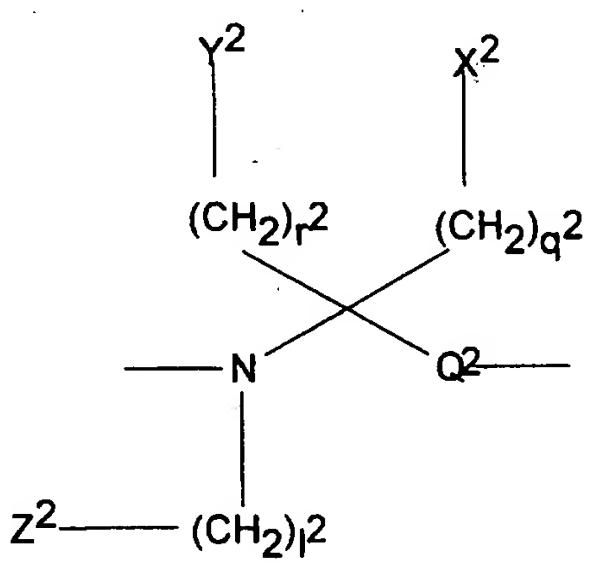
X^1 is hydrogen, isopropyl, tert. butyl, phenyl, cyclopropyl, cyclohexyl, 2-hydroxyethyl, or amino,

Y^1 is hydrogen, or methyl,

Z^1 is hydrogen.

3. The compound according to claim 2 wherein A is the residue of leucine, isoleucine, valine, phenylalanine, cyclohexylalanine or homophenylalanine, preferably leucine.

4. The compound according to any one of the preceeding claims wherein B is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

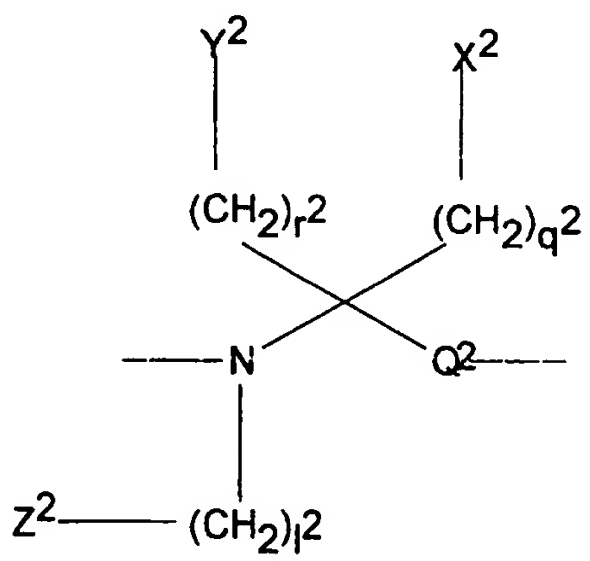
X^2 is hydrogen, phenyl, amino, guanidino, hydroxy, isopropyl, carboxy

Y^2 is hydrogen, or methyl,

Z^2 is hydrogen,
or the residue of any of the following, non-proteinogenic amino acids; dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-aminobutyric acid, beta-alanine, cis- and trans 2-aminocyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid or 4-aminomethylbenzoic acid.

5. The compound according to claim 4 wherein B is the residue of glycine, alanine, serine, lysine, ornithine, arginine, glutamic acid or aspartic acid, preferably alanine.

6. The compound according to any one of the preceeding claims wherein C is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

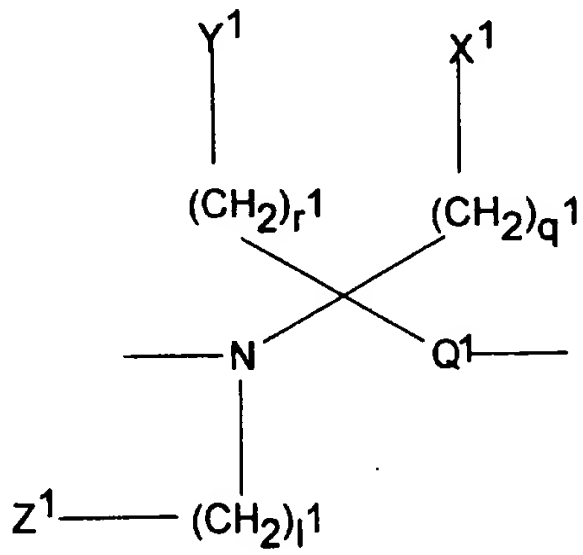
X^2 is hydrogen, imidazolyl, phenyl, amino, hydroxy, isopropyl, carboxy, amino-carbonyl,or guanidino,

Y^2 is hydrogen or methyl,

Z^2 is hydrogen.

7. The compound according to claim 6 wherein C is the residue of lysine, glutamine, glutamic acid, asparagine, aspartic acid, arginine, ornithine, serine or histidine, preferably glutamine or ornithine.

8. The compound according to any one of the preceeding claims wherein D is a non-proteinogenic or proteinogenic amino acid of the general formula II



formula II

wherein Q^1 is $-CH_2-$ or -CO-,

l^1 and r^1 are 0 , q^1 is 0, 1, 2, 3, or 4,

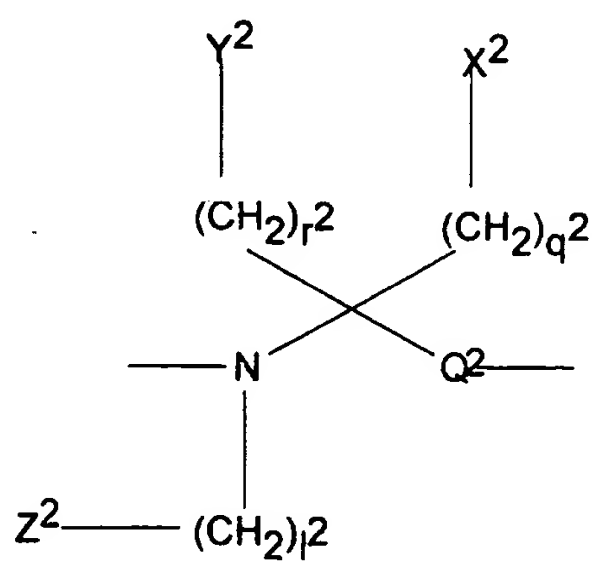
X^1 is hydrogen, isopropyl, tert. butyl, phenyl, cyclopropyl, cyclohexyl, 2-hydroxy-ethyl, or amino,

Y^1 is hydrogen, or methyl,

Z^1 is hydrogen.

9. The compound according to claim 8 wherein D is the residue of leucine, isoleucine, valine, phenylalanine, cyclohexylalanine or homophenylalanine, preferably leucine.

10. The compound according to any one of the preceeding claims wherein E is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

X^2 is hydrogen, phenyl, amino, guanidino, hydroxy, isopropyl, carboxy,

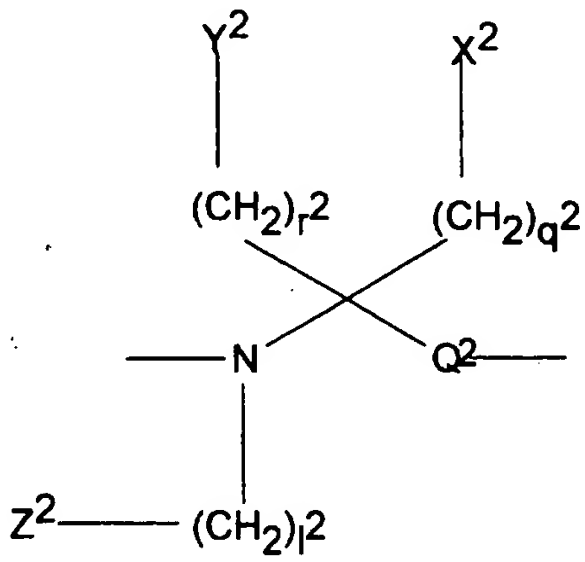
Y^2 is hydrogen, or methyl,

Z^2 is hydrogen,

or the residue of any of the following, non-proteinogenic amino acids; dehydroalanine, anthranilic acid, 3-aminobenzoic acid, 4-aminobenzoic, 4-amino-butyric acid, beta-alanine, cis- and trans 2-aminocyclohexanecarboxylic acid, 4-aminomethylcyclohexanecarboxylic acid or 4-aminomethylbenzoic acid.

11. The compound according to claim 10 wherein E is the residue of glycine, alanine, serine, threonine, tyrosine, lysine, ornithine, glutamic acid, aspartic acid, homoarginine or arginine, preferably serine.

12. The compound according to any one of the preceeding claims wherein z is 1 and F is a non-proteinogenic or proteinogenic alpha amino acid residue of the general formula III



formula III

wherein Q^2 is $-CH_2-$ or -CO-,

l^2 and r^2 are 0, q^2 is 0, 1, 2, 3, or 4,

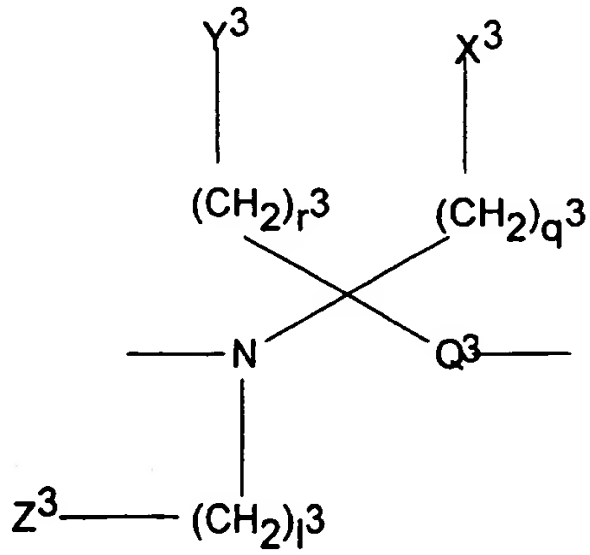
X^2 is hydrogen, phenyl, amino, hydroxy, isopropyl, carboxy, aminocarbonyl, or guanidino,

Y^2 is hydrogen or methyl,

Z^2 is hydrogen.

13. The compound according to claim 12 wherein F is the residue of alanine, phenylalanine, glycine, serine, valine, lysine, glutamine, glutamic acid, asparagine, aspartic acid or arginine, preferably alanine.

14. The compound according to any one of the preceeding claims wherein G is a non-proteinogenic or proteinogenic amino acid residue of the general formula IV



Formula IV

wherein Q^3 is $-CH_2-$ or -CO-,

l^3 and r^3 are 0, q^2 is 0, 1, 2, 3, or 4,

X^2 is amino, methylamino, dimethylamino, amidino, benzamidino, guanidino, imidazolyl, hydroxy, aminocarbonyl,

Y^2 is hydrogen or methyl,

Z^2 is hydrogen.

15. The compound according to claim 14 wherein G is the residue of arginine, lysine, glutamine, ornithine, histidine, serine or asparagine, preferably arginine.

16. The compound according to any one of the preceeding claims wherein M is the residue of valine, isoleucine, leucine, penicillamine, lysine, glutamic acid, glutamine, aspartic acid, arginine, alanine, cysteine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

17. The compound according to any one of the claims 1-15 wherein M is a dipeptide residue and the amino acid residue in the aminoterminal position of the dipeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, aspartic acid or ornithine, the amino acid residue in the second position of the dipeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

18. The compound according to any one of the claims 1-15 wherein M is a tripeptide residue and the amino acid residue in the aminoterminal position of the tripeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the second position of the tripeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the third position of the dipeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

19. The compound according to any one of the claims 1-15 wherein M is a tetrapeptide residue and the amino acid residue in the aminoterminal position of the tetrapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenyl-alanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the second position of the tetrapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the third position of the tetrapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid; the amino acid residue in the fourth position of the tetrapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

20. The compound according to any one of the claims 1-15 wherein M is a pentapeptide residue and the amino acid residue in the aminoterminal position of the pentapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the second position of the pentapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the third position of the pentapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-amino-phenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the fourth position of the pentapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the fifth position of the pentapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

21. The compound according to any one of the claims 1-15 wherein M is a hexapeptide residue and the amino acid residue in the aminoterminal position of the hexapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the second position of the hexapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the third position of the hexapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-

naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the fourth position of the hexapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-amino-phenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the fifth position of the hexapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the sixth position of the hexapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

22. The compound according to any one of the claims 1-15 wherein M is a heptapeptide residue and the amino acid residue in the aminoterminal position of the heptapeptide is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the second position of the heptapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the third position of the heptapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the fourth position of the heptapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the fifth position of the heptapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-amino-

phenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the sixth position of the heptapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the seventh position of the heptapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

23. The compound according to any one of the claims 1-15 wherein M is an octapeptide residue and the amino acid residue in the aminoterminal position of the octapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the second position of the octapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the third position of the octapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the fourth position of the octapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the fifth position of the octapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the sixth position of the octapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the

seventh position of the octapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the eighth position of the octapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

24. The compound according to any one of the claims 1-15 wherein M is a nonapeptide residue and the amino acid residue in the aminoterminal position of the nonapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the second position of the nonapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthyl-alanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the third position of the nonapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the fourth position of the nonapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the fifth position of the nonapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the sixth position of the nonapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the seventh position of the nonapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid,

aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the eighth position of the nonapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the ninth position of the nonapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

25. The compound according to any one of the claims 1-15 wherein M is a decapeptide residue and the amino acid residue in the aminoterminal position of the decapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in the second position of the decapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the third position of the decapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the fourth position of the decapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the fifth position of the decapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the sixth position of the decapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the seventh position of the decapeptide residue

is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the eighth position of the decapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-amino-phenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the ninth position of the decapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the tenth position of the decapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

26. The compound according to any one of the claims 1-15 wherein M is an undecapeptide residue and the amino acid residue in the aminoterminal position of the undecapeptide residue is the residue of asparagine, glutamine, serine, aspartic acid, glutamic acid, lysine, alanine, threonine, methionine, arginine, histidine or leucine, preferably aspartic acid, the amino acid residue in the second position of the undecapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in the third position of the undecapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the fourth position of the undecapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclo-hexylalanine or lysine, preferably phenylalanine, the amino acid residue in the fifth position of the undecapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid,

glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the sixth position of the undecapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the seventh position of the undecapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the eighth position of the undecapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the ninth position of the undecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the tenth position of the undecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the eleventh position of the undecapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

27. The compound according to any one of the claims 1-15 wherein M is an dodecapeptide residue and the amino acid residue in the aminoterminal position of the dodecapeptide residue is the residue of alanine, valine, leucine, serine, threonine, lysine, cysteine, glutamine, glutamic acid, asparagine, aspartic acid, glycine, N-methylalanine or histidine, preferably alanine or N-methylalanine, the amino acid residue in the second position of the dodecapeptide residue is the residue of asparagine, glutamine, serine, aspartic acid, glutamic acid, lysine,

alanine, threonine, methionine, arginine, histidine or leucine, preferably aspartic acid, the amino acid residue in the third position of the dodecapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in the fourth position of the dodecapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the fifth position of the dodecapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the sixth position of the dodecapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the seventh position of the dodecapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine, preferably aspartic acid, glutamine or ornithine, the amino acid residue in the eighth position of the dodecapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the ninth position of the dodecapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthyl-alanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the tenth position of the dodecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the eleventh position of the dodecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the twelvth position of the dodecapeptide residue is

the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

28. The compound according to any one of the claims 1-15 wherein M is an tredecapeptide residue and the amino acid residue in the aminoterminal position of the tredecapeptide residue is the residue of tyrosine, histidine, phenylalanine, tryptophane, lysine, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, glutamine or asparagine, preferably tyrosine, the amino acid residue in the second position of the tredecapeptide residue is the residue of alanine, valine, leucine, serine, threonine, lysine, cysteine, glutamine, glutamic acid, asparagine, asparticacid, glycine, N-methylalanine or histidine, preferably alanine or N-methylalanine, the amino acid residue in the third position of the tredecapeptide residue is the residue of asparagine, glutamine, serine, aspartic acid, glutamic acid, lysine, alanine, threonine, methionine, arginine, histidine or leucine, preferably aspartic acid, the amino acid residue in the fourth position of the tredecapeptide residue is the residue of alanine, valine, serine, leucine, lysine, threonine, glycine, glutamine, asparagine or histidine, preferably alanine or asparagine, the amino acid residue in the fifth position of the tredecapeptide residue is the residue of isoleucine, leucine, valine, alanine, threonine, phenylalanine or methionine, preferably isoleucine, the amino acid residue in the sixth position of the tredecapeptide residue is the residue of phenylalanine, tyrosine, tryptophane, histidine, 1-naphthylalanine, 2-naphthylalanine, cyclohexylalanine or lysine, preferably phenylalanine, the amino acid residue in the seventh position of the tredecapeptide residue is the residue of threonine, serine, lysine, methionine, leucine, isoleucine, alanine, asparagine, glutamine, aspartic acid, glutamic acid, cysteine or histidine, preferably threonine, the amino acid residue in the eighth position of the tredecapeptide residue is the residue of asparagine, aspartic acid, glutamine, glutamic acid, serine, lysine, alanine, threonine, cysteine or ornithine,

preferably aspartic acid, glutamine or ornithine, the amino acid residue in the ninth position of the tredecapeptide residue is the residue of serine, alanine, cysteine, threonine, lysine, valine, asparagine, aspartic acid, glutamine or glutamic acid, preferably alanine, the amino acid residue in the tenth position of the tredecapeptide residue is the residue of tyrosine, phenylalanine, histidine, glutamine, lysine, tryptophane, 1-naphthylalanine, 2-naphthylalanine, biphenylalanine, alanine, glutamic acid or cysteine, preferably tyrosine, the amino acid residue in the eleventh position of the tredecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, serine, glutamic acid, aspartic acid, cysteine, 4-aminophenylalanine, 4-guanidinophenylalanine or asparagine, preferably arginine, the amino acid residue in the twelvth position of the tredecapeptide residue is the residue of lysine, arginine, ornithine, histidine, glutamine, alanine, glutamic acid, aspartic acid, asparagine, cysteine or serine, preferably lysine, ornithine or aspartic acid, the amino acid residue in the thirteenth position of the tredecapeptide residue is the residue of valine, isoleucine, leucine, penicillamine, lysine, cysteine, glutamic acid, glutamine, aspartic acid, arginine, alanine, homocysteine, leucine, isoleucine, methionine, ornithine, phenylalanine or threonine, preferably valine.

29. The compound according to any one of the claims 1-15 wherein N is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine.

30. The compound according to any one of the claims 1-15 wherein N is a dipeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the

carboxyterminal position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine.

31. The compound according to any one of the claims 1-15 wherein N is a tripeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the carboxyterminal position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine:

32. The compound according to any one of the claims 1-15 wherein N is a tetrapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the carboxyterminal position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or

leucine, preferably glutamine.

33. The compound according to any one of the claims 1-15 wherein N is a pentapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the carboxyterminal position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine.

34. The compound according to any one of the claims 1-15 wherein N is a hexapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine,

preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the carboxyterminal position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine.

35. The compound according to any one of the claims 1-15 wherein N is a heptapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine, the amino acid residue in the carboxyterminal position

is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine.

36. The compound according to any one of the claims 1-15 wherein N is an octapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine, the amino acid residue in the seventh position is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine, the amino acid residue in the carboxyterminal position is the residue of serine, threonine, alanine, cysteine, asparagine, aspartic acid, glutamic acid, glutamine, histidine, arginine, tyrosine or homocysteine.

37. The compound according to any one of the claims 1-15 wherein N is a nonapeptide residue and the amino acid residue in the first position is the residue of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably histidine or lysine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine, the amino acid residue in the seventh position is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine, the amino acid residue in the eighth position is the residue of serine, threonine, alanine, cysteine, asparagine, aspartic acid, glutamic acid, glutamine, histidine, arginine, tyrosine or homocysteine, the amino acid residue in the carboxyterminal position is the residue of arginine, lysine, ornithine, histidine, glutamine, glutamic acid, asparagine, aspartic acid, serine, tyrosine, homocysteine or alanine.

38. The compound according to any one of the claims 1-15 wherein N is a decapeptide residue and the amino acid residue in the first position is the residue

of lysine, histidine, ornithine, arginine, glutamine, glutamic acid, aspartic acid, asparagine, serine, alanine, cysteine, tyrosine, tryptophane, phenylalanine or homocysteine, preferably lysine or histidine, the amino acid residue in the second position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the third position is the residue of leucine, alanine, cyclohexylalanine, glutamic acid, lysine, aspartic acid, cysteine, valine, isoleucine, methionine, histidine, threonine or phenylalanine, preferably leucine, the amino acid residue in the fourth position is the residue of glutamine, glutamic acid, aspartic acid, asparagine, lysine, serine, arginine, ornithine, histidine, cysteine, methionine, threonine, tyrosine, alanine or leucine, preferably glutamine, the amino acid residue in the fifth position is the residue of asparagine, histidine, glutamine, aspartic acid, glutamic acid, lysine, ornithine, serine, methionine, threonine or alanine, preferably histidine, the amino acid residue in the sixth position is the residue of isoleucine, valine, threonine, glutamic acid, aspartic acid, lysine, cysteine, penicillamine, homocysteine, methionine, histidine, leucine or alanine, the amino acid residue in the seventh position is the residue of methionine, norleucine, homocysteine, leucine, glutamine, glutamic acid, aspartic acid, lysine, ornithine, histidine, threonine, asparagine, alanine or serine, the amino acid residue in the eighth position is the residue of serine, threonine, alanine, cysteine, asparagine, aspartic acid, glutamic acid, glutamine, histidine, arginine, tyrosine or homocysteine, the amino acid residue in the ninth position is the residue of arginine, lysine, ornithine, histidine, glutamine, glutamic acid, asparagine, aspartic acid, serine, tyrosine, homocysteine or alanine, the amino acid residue in the carboxyterminal position is the residue of glutamine, glutamic acid, histidine, lysine, asparagine, aspartic acid, arginine, serine, threonine or tyrosine.

39. The compound according to any one of the preceeding claims wherein K is

hydrogen or a group of formula W^1-$(CH_2)_{v1}$-CO-, wherein W^1 is hydrogen, hydroxy or C_{1-6}-alkyl, preferably hydrogen, and v^1 is 0, 1, 2, 3 or 4, preferably 1.

40. The compound according to any one of the preceeding claims wherein L is

, wherein p^6 and p^7 independently are 0, 1 or 2, preferably 0; W^6 is hydrogen, hydroxy or C_{1-6}-alkyl, preferably hydrogen; p^8 is 0 or 1, preferably 0; W^7 is hydrogen, hydroxy or C_{1-6}-alkyl, preferably hydrogen.

41. A compound according to claim 1 selected from the group comprising:

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2,

Asp-Ala-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2,

Asp-Tyr-Arg-Ala-Val-Leu-Ala-Gln-Leu-homoArg-His-NH_2,

Asp-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Cyclo(Glu^9-Lys^{13})-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Lys-His-NH_2,

Cyclo(Lys^5-Glu^9)-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Tyr-Arg-Lys-Val-Leu-Glu-Gln-Leu-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Phe-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Phe-Ser-Ala-Arg-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Tyr-Ala-Arg-His-NH_2,

Asp-Ala-Gln-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Glu-Val-Leu-Arg-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Cyclo(Asp^1-[Gly]-Orn^5)-Asp-Ala-Tyr-Arg-Orn-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Lys-His-NH_2,

Ac-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Lys-His-NH_2,

Cyclo(Lys^2-Glu^6)-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2,

Cyclo(Lys^4-Glu^8)-Lys-Val-Leu-Lys-Gln-Leu-Ser-Glu-Arg-NH_2,

Cyclo(Orn^2-[$COCH_2$]-Pen^6)-(Asp-Orn-Tyr-Arg-Lys-Pen-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-NH_2

Cyclo(Lys^3-Glu^7)-Lys-Val-Leu-Lys-Gln-Leu-Ser-Glu-Arg-His-NH_2

Cyclo(Lys^2-Glu^6)-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys^3-Glu^7)-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Glu^1-Lys^5)-Glu-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys^4-Glu^8)-Asp-Ala-Tyr-Lys-Lys-Val-Leu-Glu-Gln-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys^3-Glu^7)-Ala-Tyr-Lys-Lys-Val-Leu-Glu-Gln-Leu-Ser-Ala-Arg-His-NH_2

Cyclo(Lys^4-Glu^8)-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Glu-Leu-Ser-Ala-Arg-His-NH_2 and

Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-NH_2; or a pharmaceutically acceptable salt thereof.

42. A compound according to claim 1 selected from the group comprising:

H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-His-NH_2,

Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Ac-Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp^2-[Gly]-Orn^6)-Ac-Asp-Asp-Ile-Phe-Thr-Orn-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp^6-[Gly]-Orn^{10})-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Orn-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Cyclo(Asp^{10}-[Gly]-Orn^{14})-Ac-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Asp-Val-Leu-Ala-Orn-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

Ac-(N-Me)Ala-Asp-Ala-Ile-Phe-Thr-Asp-Ala-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-His-NH_2,

or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition comprising, as an active ingredient, a compound

according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

44. The composition according to claim 43 in unit dosage form, comprising from about 10 to about 200 mg of the compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof.

45. A pharmaceutical composition for stimulating the release of growth hormone from the pituitary, the composition comprising, as an active ingredient, a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

46. A pharmaceutical composition for administration to animals to increase their rate and extent of growth, to increase their milk and wool production, or for the treatment of ailments, the composition comprising, as an active ingredient, a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

47. A method of stimulating the release of growth hormone from the pituitary, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof or of a composition according to any one of the preceeding composition claims.

48. The method according to claim 47, wherein the effective amount of the compound according to any one of the preceeding compound claims or

pharmaceutically acceptable salt or ester thereof is in the range of from about 0.0001 to about 100 mg/kg body weight per day, preferably from about 0.001 to about 50 mg/kg body weight per day.

49. A method for increasing the rate and extent of growth of animals to increase their milk and wool production, or for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof or of a composition according to any one of the preceeding composition claims.

50. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

51. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for stimulating the release of growth hormone from the pituitary.

52. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for administration to animals to increase their rate and extent of growth, to increase their milk and wool production, or for the treatment of ailments.

53. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment or prevention of catabolic side effects of glucocorticoids, osteoporosis, retardation, wounds, bone fractures, growth retardation, renal failure or insufficiency resulting in growth retardation, physiological short stature including growth hormone deficient children and short stature associated with chronic illness, obesity and growth

retardation associated with obesity, growth retardation associated with the Prader-Willi syndrome and Turner@s syndrome; burns; intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushings syndrome; osteochondrodysplasias, Noonans syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound healing and psychosocial deprivation; pulmonary dysfunction and ventilator dependency; cachexia and protein loss due to chronic illness such as cancer or AIDS, hyperinsulinemia including nesidioblastosis; adjuvant for ovulation induction; the age-related decline of thymic function; immunosuppressed patients; skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; disorder of aging in companion animals.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00175

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 14/60, A61K 38/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REG, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9411396 A1 (THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND), 26 May 1994 (26.05.94), see claims --	1-46,50-53
X	EP 0177819 A2 (F. HOFFMANN-LA ROCHE & CO. AKTIENGESELLSCHAFT), 16 April 1986 (16.04.86), see claims --	1-46,50-53
X	WO 9218531 A1 (F. HOFFMANN-LA ROCHE AG), 29 October 1992 (29.10.92), see seq 26 and 29 -- --------	1-46,50-53

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 Sept 1997	10.09.97
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez lagerlöf Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00175

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 47-49
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [X] Claims Nos.: 1-2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Due to a very large number of variable positions in the amino acid chain and the variability in the choice of amino acids in each of these positions, a full evaluation of the relevance state of the art literature has not been made. The search has therefore essentially been restricted to positions and amino acids supported by claims 3,5,7,9,11, 13 and 15.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/08/97

International application No.
PCT/DK 97/00175

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411396 A1	26/05/94	AU 5668894 A	08/06/94
EP 0177819 A2	16/04/86	SE 0177819 T3	
		AU 589373 B	12/10/89
		AU 4768385 A	10/04/86
		CA 1270598 A	19/06/90
		DE 3585867 A	21/05/92
		DK 433485 D	00/00/00
		IE 59240 B	26/01/94
		JP 61118400 A	05/06/86
		US 4622312 A	11/11/86
		US 4649131 A	10/03/87
		US 4734399 A	29/03/88
WO 9218531 A1	29/10/92	AU 662731 B	14/09/95
		AU 1448592 A	17/11/92
		CA 2084061 A	10/10/92
		EP 0525838 A	03/02/93
		EP 0542937 A	26/05/93
		IL 101452 A	14/11/96
		NZ 242209 A	27/04/94